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Division of

RESOURCES, CENTERS & COMMUNITY ACTIVITIES

1982 Annual Report
October 1, 1981-September 30, 1982

U.S. DEPARTMENT
OF HEALTH
AND HUMAN SERVICES

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DIVISION OF RESOURCES, CENTERS, AND COMMUNITY ACTIVITIES
NATIONAL CANCER INSTITUTE

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I.

OFFICE OF THE DIRECTOR

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DIRECTOR'S REPORT

The Division of Resources, Centers, and Community Activities (DRCCA) is emphasizing a dynamic new course which links cancer control and prevention research with program activities. A system of classifying cancer control research into phases will help focus and monitor progress. Developing or testing specific actions or interventions aimed at having population impacts on important cancer problems are the major priority. This new quantitative approach will assist in translating the major strides in clinical and basic laboratory research into a measurable decline of cancer incidence and mortality in coming years.

DRCCA is one of five Divisions within the National Cancer Institute (NCI) and is comprised of three principal areas-(1) preventive medicine (2) centers and community oncology, and (3) cancer control applications. The Division has the principal Federal responsibility for assuring--

- research and development for applied cancer prevention and control, including chemoprevention, diet and cancer, occupational cancer, early detection, behavioral medicine/smoking and cancer, and other aspects of cancer prevention and control,

- the rapid and effective utilization of cancer research findings in prevention, detection, diagnosis, and treatment of cancer,

- the development of a national system of cancer centers and community oncology programs,

- the management of research programs focused on developing new knowledge concerning cancers of particular organs,

- the development of educational research and the evaluation of its relevance to cancer and the management of training programs for clinical oncologists and cancer research scientists, and

- the development of plans for necessary construction of laboratory and clinical research facilities.

Highlights of DRCCA activities include:

- Initiating management procedures to assure DRCCA Board of Scientific Counselors review of all major existing and proposed programs.

- Bringing on key new staff who have a wide range of research and management experience in clinical oncology, cancer control, and preventive medicine.

- Developing a new chemoprevention research program to determine whether selected micronutrients or synthetic compounds can be shown in human trials to reduce cancer incidence.

- Planning for a more extensive control effort in relation to smoking, nutrition, and occupation.

- Establishing a community clinical oncology program to promote cooperation among community physicians, cancer centers, and other research bases.

- Conducting cooperative efforts with cancer centers to maintain excellence in research, control, and education remain a priority for DRCCA. The Cancer Centers Program continues as a focal point for the National Cancer Program

- Fostering interdisciplinary research directed toward increased understanding of the etiology, detection, diagnosis, prevention, or treatment of cancer at specific sites where levels of research activity have not been commensurate with the morbidity and mortality caused by the diseases.

- Sponsoring a joint working conference between the National Cancer Institute and the National Institute on Aging (NIA) on issues in the prevention and treatment of cancer in the elderly.

- Creating Cancer Control Research Units and Science Projects to encourage study of how best to apply new knowledge in the prevention and treatment of cancer in such a way as to achieve measurable population impacts.

- Designing a new classification system of phases of cancer control research which provides an orderly sequence from basic or clinical research through cancer control research to widespread population benefits.

The Chemoprevention Research Program rationale stems from advances in laboratory research on carcinogenesis inhibition and complementary data from epidemiology. This is one of our most promising areas for cancer prevention research. Potential chemopreventive agents include several naturally occurring substances found in many foods, such as vitamin A and its precursor beta-carotene, vitamins C, E, and the trace metal selenium. These will be the first compounds studied in human trials. Synthetic analogs of vitamin A and other cancer inhibitors such as phenolic antioxidants, protease inhibitors, prostaglandin synthesis inhibitors and indoles are a current laboratory focus. Tracking of consumption and cancer incidence patterns related to chemoprevention hypotheses also is important to the chemoprevention program.

Complementary to the chemoprevention research thrust, the diet and cancer program shall emphasize methods of nutritional assessment for population studies. This shall allow better testing of current hypotheses related to fat, fiber, vegetables, and other components of our diet. The National Cancer Advisory Board and the DRCCA Board of Scientific Counselors have stressed the need for a greater diet and cancer research effort. In a DRCCA sponsored study, the National Academy of Sciences has reviewed current evidence, made interim recommendations to the public, and is in the process of considering future research needs.

The Community Clinical Oncology Program (CCOP) has now begun, after extensive consultation during program development with community physicians. This cancer control effort shall bring advantages of clinical research to cancer patients

in their own communities. Practicing physicians and their patients will have the opportunity to participate in clinical research protocols thus fostering a dynamic interaction between community physicians and those at research centers to the benefit of cancer control. CCOP shall provide a basis for studying the diffusion of cancer therapy throughout medical practice. The networks established should serve as an excellent resource for future NCI-sponsored cancer control and prevention research activities.

The principal purpose of cancer centers is to extend knowledge and understanding of the causes, mechanisms, diagnosis, and treatment of the multiple forms of cancer through the development of either specialized or broad multidisciplinary programs in basic clinical cancer research. They constitute a national resource providing a critical core of: (1) highly trained laboratory and clinical research personnel; (2) physical facilities and equipment; and (3) administrative support structures. These three important elements facilitate the generation of new knowledge about cancer and accelerate transfer of new information about cancer prevention, diagnosis, treatment, rehabilitation, and continuing care to health professionals in their surrounding communities and to the general public.

The Organ Sites Program consists of grant supported projects of targeted and coordinated cancer research encompassing the epidemiologic, laboratory, and clinical modes. Currently, there are organ site projects concerned with cancer of the urinary bladder, large bowel, pancreas, and prostate. Each site represents a major public health problem and yet there has been comparatively little research, particularly at the preclinical level. The breast cancer program will be transferred to this division. It will continue its multidisciplinary research activities in the laboratory and the clinic with the aim of increasing our understanding and improving methods regarding the etiology, epidemiology, diagnosis, prognosis, treatment, or prevention of breast cancer.

The collaborative working conference between NCI and NIA was a significant first step to develop information that could be used to improve treatment and control of cancer for older Americans. This activity represented a DRCCA cancer control effort to extend the national commitment to cancer research to include the growing national concern for the older segment of our population.

With the new knowledge learned within the past decade, it is now more realistic than ever to build a cancer control program that will lead to a measurable decline in cancer incidence and mortality. We are enthusiastic about being able to work together with our advisory bodies and with physicians and scientists throughout the country toward this end. Our aim is to assure that the new DRCCA programs shall be key contributors to the success of the Nation's cancer effort as a whole.

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Chemoprevention Program

Purpose and Objectives

Cancer chemoprevention, a priority research area in the Division of Resources, Centers and Community Activities (DRCCA), is aimed at testing the concept that certain natural or synthetic agents may lower cancer incidence. Potential chemopreventive agents include several naturally occurring substances already in public use, such as vitamin A and its precursor beta-carotene, ascorbic acid (vitamin C), alpha-tocopherol (vitamin E) and the trace metal, selenium (Se), as well as others still in the realm of the laboratory such as phenolic and prostaglandin synthesis inhibitors.

Current research data, collected largely from laboratory studies, suggest that chemopreventive agents have the capacity to inhibit the neoplastic effects of chemical carcinogens and may prevent, inhibit, retard or reverse one or more of the stages of carcinogenesis. For example, laboratory studies indicate that chemopreventive agents (e.g. retinoids) can inhibit the expression of the transformed cell state in a number of *in vitro* cell culture systems as well as prevent the development of cancers (including skin, bladder, trachea and mammary gland) in a number of *in vivo* animal systems.

Although still few in number, epidemiological studies related to chemoprevention, suggest that humans may have lower risks of cancer associated with the consumption of these chemopreventive substances. Several studies, for example, suggest a reduced risk of lung cancer for male smokers with higher intakes of vitamin A in their diets. Other epidemiological studies suggest that ascorbic acid may have a beneficial effect in preventing upper gastrointestinal tract cancers.

The Chemoprevention Program is committed to support studies in two major research areas:

- epidemiological investigations involving consumption and usage of micronutrients and chemopreventive agents and clinical trials of selected agents in risk populations, and

- investigations directed at examining the safety and toxicity of various substances and their application both prior to initiating human intervention studies and during their course.

Background and History of the Chemoprevention Program

At the first meeting of DRCCA's Board of Scientific Counselors on September 18-19, 1980, a Chemoprevention Task Force was established as a subcommittee to the Board. The purpose of this Task Force was to recommend to the Director, NCI, through the Director, DRCCA, whether the chemoprevention research endeavors should exist as a separate program. The Task Force convened January 28, 1981, and conducted three subsequent workshops (May, June and September) with invited speakers to assess the state-of-the-art of chemoprevention by reviewing hypotheses and data from both laboratory and human studies.

The May 1981 workshop focused on those agents which are potentially available for immediate use in clinical studies and included beta-carotene, ascorbic acid

alpha-tocopherol and selenium. Data from studies using synthetic retinoids, phenolic inhibitors, protease inhibitors and prostaglandin synthesis inhibitors were discussed at a June 1981 workshop. At the September meeting, protocols from eleven chemoprevention clinical studies were reviewed. The recommendations resulting from these workshops were that intervention trials using chemoprevention should be initiated, but with care to see that toxicity and safety issues were adequately addressed. It was also recognized that additional research was needed in all areas including laboratory, epidemiological and clinical investigation.

With the appointment of Dr. Peter Greenwald as Director, DRCCA, the Chemoprevention Program was initiated. A core of staff members meet with the Director on a regular basis to coordinate and provide direction to the Chemoprevention Program until the permanent staff are recruited. Both short and long-range planning activities have begun and a number of research activities have been initiated. Staff recruitment and hiring is underway.

Program Accomplishments

During this initial year extramural accomplishments have included:

- Chemoprevention Referral Guidelines

  Referral guidelines which are used to assign appropriate grant applications to DRCCA (prepared for the Division of Research Grants) were presented to the Board of Scientific Counselors, January 1982, for comments and suggestions. These referral guidelines include all categories of chemoprevention agents--those currently available to the public such as ascorbic acid, and alpha-tocopherol, and those still in the laboratory such as protease and prostaglandin synthesis inhibitors. Research areas include epidemiological and clinical studies, as well as those studies concerning toxicity and agent application. Some appropriate research topics for DRCCA are to:

  identify populations at risk of developing cancer to study the effect that chemopreventives have on cancer incidence

  design and conduct clinical trials to test for efficacy of agents in inhibiting the onset of or retardation of the progress of pre-neoplastic changes, and

  examine the long term toxicity of dosing with various agents in appropriate models (animal and human).

  Grant applications which fulfill these guidelines are presently referred to the Chemoprevention Program. A mechanism is in place to have the applications reassigned if not appropriate for DRCCA.

- Request for Application (RFA): The Role of Natural Inhibitors in the Prevention of Cancer

  Approximately $2 million has been allocated to support studies in response to the above RFA which will examine the role of several natural inhibitors including beta-carotene, ascorbic acid, alpha-tocopherol

and the trace metal selenium in the prevention of cancer. This RFA was issued in March 1982 with a June 15 deadline for grant application submission. Proposed studies under this RFA should:

- o elucidate the protective effect of natural inhibitors in reducing the incidence of various site specific cancers, and
- o lead to a greater understanding of the extent or action of several natural inhibitors in the possible cancer prevention process in humans.

These studies may include case-control studies as well as cohort studies and risk reduction clinical trials. Safety and adverse health effects are to be studied also.

A favorable response to this RFA by the scientific community was evidenced by the receipt of approximately 70 Letters of Intent. Potential grant applications include intervention studies, cohort studies and case-control studies. At the end of year three of these grants, answers are expected on the possible benefits of naturally occurring micronutrients and on the potential toxicity from megavitamin use depending on studies proposed. Also expected at this time are early results from human trials with synthetic analogs in preventing the recurrence of primary skin cancers or the progression of precursor lesions to cancer.

- o A Randomized Trial of Aspirin and Mortality in U.S. Physicians - Dr. Charles Hennekens

The National Cancer Institute and the National Heart, Lung, and Blood Institute are jointly sponsoring a five-year clinical trial to determine the usefulness of beta-carotene and aspirin in the primary prevention of cancer and cardiovascular disease, respectively. Approximately 22,000 healthy U.S. physicians, 40-75 years of age, are being invited to participate in the trial. The principal investigator is Dr. Charles Hennekens of Harvard Medical School.

Each participant will take one pill daily. On even days the tablet will contain either aspirin or a placebo; on odd days the preparation will contain either beta-carotene or a placebo. For convenience the pills will be supplied in calendar packs. Every six months each participant will be sent a new supply of pills together with a follow-up questionnaire on which to report compliance with the regimen and current health status. Randomization of the physicians to study subgroups is expected to begin in the Fall of 1982.

- o Program Planning

Chemoprevention staff and members of NCI's Office of Program Planning and Evaluation have developed an operational plan for a comprehensive NCI Chemoprevention Program. This is a systematic approach to program development through identification of program objectives and decision criteria, with "sub-flows" to achieve the desired objectives. Each sub-flow identifies a logical arrangement of major research elements followed by a decision point before proceeding to the next stage. Finalization of the plan is expected by October, 1982.

Program Projections

Following are extramural and intramural program plans projected for 1982 and 1983.

- o National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Survey

  From 1971-1975, 14,407 persons were interviewed by the National Center for Health Statistics about their health and nutritional status. They also received a battery of medical and laboratory examinations including an assay for serum vitamin A levels. These individuals, whose ages range from 25-74, comprise a representative sample of the U.S. population.

  The Division will enter into an Intraagency Agreement with the National Center for Health Statistics which is conducting a follow-up survey of these individuals, in collaboration with NIH components, to investigate the relationships between nutritional factors and the incidence and mortality of cancer. This follow-up survey has advantages not found in other cohort studies. The sample is large and geographically heterogenous; it is diverse in terms of social and economic characteristics. Epidemiological findings of the follow-up will be more representative of the U.S. population compared to other studies which are usually considerably smaller in size and scope. On May 7, 1982, DRCCA's Board of Scientific Counselors approved the concept of this study which will begin in the latter part of 1982.

- o Clinical Chemistry Laboratory and Quality Assurance Center

  The Chemoprevention Program will undertake a number of studies to examine the role of natural and synthetic inhibitors, including but not limited to beta-carotene, vitamin A and its analogs, vitamins C and E and selenium, in reducing the incidence of site specific cancers.

  The above Center will be initiated under contract to support the Division's analytical requirements. A major role of the contract will also be to facilitate the quality of these chemopreventive substances since they are not routine analyses carried out by prospective grantees. The contractor will provide a quality control and assurance program, assist in standardizing analytical methodology for contractors and grantees participating in the program, and provide advice and consultation to program participants concerning sampling, storage, and analytical results from various participating laboratories.

  This concept was presented to and approved by the Board of Scientific Counselors on May 7, 1982. It is expected that one or more contracts will be awarded for a three-year period beginning in the latter part of 1982.

- o Cancer Among Aspirin Myocardial Infarction Study Subjects

  Sera collected from participants in the Aspirin Myocardial Infarction Study (AMIS) will be analyzed to determine whether pre-disease levels of beta-carotene, retinol, retinol-binding protein, alpha-tocopherol

and selenium are related to the subsequent development of cancer. Among the 4,524 men and women who enrolled in AMIS, 107 reported the occurrence of cancer during their participation in the trial. The initial study was sponsored by the National Heart, Blood, and Lung Institute. Through an Interagency Agreement, the Center for Disease Control will collaborate with DRCCA in analyzing these samples. As part of the study, the effect of thawing and refreezing sera will be assessed by comparing baseline retinol levels in the random half of patients whose sera were invaded for other analyses with those whose sera remained frozen since baseline.

The concept for this study was reviewed and approved by the Board of Scientific Counselors on May 7, 1982.

o DRCCA Intramural Studies

The ultimate goals of the Chemoprevention Program is to test the efficacy of various agents, either natural or synthetic, in reducing cancer incidence. Several controlled human intervention trials of selected chemopreventive agents are planned. Populations to be examined will be selected on the basis of their cancer risks, environmental exposures and the extent of knowledge indicating a potential for inhibiting cancer at specific sites by specific agents. Important aspects of the program involve the assessment of the current consumption of micronutrients, consideration of human study subjects in this type of trial, and efficiency of study design.

Timetable For Progress

The Chemoprevention Program aims at the end of the second year to have results from the retrospective studies using sera banks; by the third year to have clear results on the possible benefits of naturally occurring micronutrients, including vitamins, and on potential toxicity from megavitamin use. Early results of human trials with the synthetic analogs might also be expected by year 3; in years 4-6 we expect results of human trials involving the synthetic agents which will include studies of high risk groups and major cancer sites.

Staff Publications

Sestili, M.A., Norris, J.S., Lipshultz, L.I., and Smith, R. G.: Dunning adenocarcinoma in tissue culture: isolation of a cloned cell line, R3327H-G8-A1. Journal of Urology. 127:823-825, 1982.

La Rosa, J.H., Feinleib, M., Hoops, D., Schreiber, G.B.: Training in Epidemiology for the Occupational Physician. Journal of Occupational Medicine. 24:3, 237, 1982.

Ward, G.W., Morrison, W., Schreiber, G.: Pilot study of health professionals' awareness and opinions of the hypertension information in the mass media they use. Public Health Reports. 92:2, 113, 1982.

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Nutrition Coordinating Activities

Nutrition and nutrition-related research have been an important part of the National Cancer Institute's (NCI) activities for many years. In response to the 1974 amendments to the National Cancer Act, the Diet, Nutrition and Cancer Program (DNCP) was established within the NCI to develop and disseminate information related to the role of diet and nutrition in the etiology and prevention of cancer and in the treatment, long-term management, and rehabilitation of the cancer patient. The DNCP coordinates NCI activities with those of non-NCI organizations and encompasses all phases of nutrition and cancer activities: research, education, training, resource development, and demonstration projects.

From 1975 to 1978, the DNCP was administered by the Division of Cancer Cause and Prevention. In 1978, the program was reorganized and through 1980 was provided with central coordination through the Office of the Director, NCI. In 1981 responsibility for DNCP coordination was transferred to the Division of Resources, Centers and Community Activities (DRCCA). Although the program has historically been centrally coordinated, the actual direction of nutrition activities, including research, comes from the operating NCI divisions and offices. Each division retains responsibility for the programming, funding, and day-to-day management of specific nutrition projects. Representatives from the divisions serve on an Institute-wide working group to plan and coordinate program activities.

Guidance in program planning and conceptual review of program areas is the responsibility of the Advisory Committees or Boards of Scientific Counselors of each of the divisions or offices involved. Overall direction of the program is provided by the National Cancer Advisory Board.

The DNCP includes both extramural and intramural activities. The extramural projects are supported through grants and contracts. Research in etiology and prevention, cancer biology, treatment, and rehabilitation is managed by the division of Cancer Cause and Prevention, the Division of Cancer Biology and Diagnosis, the Division of Cancer Treatment, and the Division of Resources, Centers and Community Activities. Research training and activities in resource development, communications, and central program coordination are managed by the DRCCA. Future plans for DRCCA include nutrition and chemoprevention programs which will be implemented within new organizational settings within the Division. These programs will deal with research and applied aspects including epidemiologic and intervention studies.

Smoking, Cancer, and Health Program (SCHP)

The SCHP represents a number of organizational units within the NCI. The Program supports grants, contracts and intramural projects with central coordination provided by the Deputy Director of the Division of Resources, Centers, and Community Activities (DRCCA). The Program is concerned with research and demonstration activities in toxicology, epidemiology, prevention, behavior, pharmacology, education, information training and other areas appropriate to tobacco use, cancer and health.

The aim of the SCHP is to identify cancer risks associated with smoking and tobacco use and to develop strategies for prevention and cessation of tobacco-use behavior. Current activities include studies aimed at understanding the bio-behavioral dependence on smoking and tobacco use; epidemiological studies to assess health effects due to changing smoking and tobacco habits; toxicological studies to determine promoting and carcinogenic effects of constituents in both the particulate and gaseous phases of cigarettes; and biological studies to identify individuals at unusually high risk for the development of cancer. Also included are community demonstration and education programs aimed at deterring smoking behavior in children and adolescents, as well as the development of cessation programs targeted toward high risk subgroups that are not decreasing usage.

Future research attention will be given to evaluation of smoking prevention/cessation methods among blue collar workers in industries where exposure to carcinogens is likely to occur; studies monitoring changes in smoking prevalence and preference; epidemiologic and behavioral studies on smokeless tobacco use as a means of recruitment to regular tobacco smoking; and educational/media based prevention/cessation efforts with an emphasis on mass communications.

The NCI supports approximately 12 million dollars of smoking and tobacco related research through the mechanism of grants, contracts, and interagency and intramural agreements.

DRCCA Smoking and Health Activities

The Division is responsible for bio-behavioral, psychological, social, and educational research related to smoking and health. These activities cut across several branches and represent an approximate $4 million annual commitment to research and demonstration projects. These efforts include development and delivery of training courses for physicians and allied health professionals; smoking and tobacco components of the 21 Cancer Information Services; projects concerned with the cancer control implications of informal self-help approaches to smoking cessation; and projects directed at preventing the uptake of smoking by children and adolescents. Special emphasis has been placed on projects aimed at reducing the incidence of smoking among subgroups at higher than average risk for the development of cancer.

National Cancer Institute (NCI) and National Institute On Aging (NIA) Working Conference: "Perspectives On Prevention And Treatment Of Cancer In The Elderly," September 21 to 23, 1981

Under the auspices of its Cancer Control Program, DRCCA convened a working conference on problems and needs unique to the elderly for prevention, early detection, diagnosis, and management of cancer. This clinically-focused meeting was jointly sponsored by NCI and NIA and held at the Lister Hill Center, NIH campus, September 21 to 23, 1981.

The conference provided a forum for exploring ways in which geriatric physicians and oncologists can make contributions toward resolving problems of the older aged population. The conference grew out of a concern that use be made of accumulated knowledge existing at the interface of the clinical areas of cancer and aging. The 38 participants in the conference represented the fields of aging, oncology, epidemiology, and the social sciences. Speakers prepared manuscripts for a proceedings to be disseminated to community physicians and other health care professionals. This will help them to know about the important medical and social considerations involved in dealing with older persons regarding cancer prevention and treatment.

The rationale for the conference was that older citizens require special attention because of their vulnerability to cancer. Cancer affects older persons disproportionately. Also, our older population is increasing steadily, and particular attention is needed in view of the greater numbers of people of 75 years and older. This growth in the older age groups within the context of the United States health care system clearly indicates that there will be more old people who will require cancer treatment and continuing care.

The Conference Goals were to:

1) Identify, organize, and synthesize information from oncology, geriatrics, gerontology, and relevant fields concerned with improving prevention, early detection, and diagnosis of cancer in older persons; and the treatment, care, and recovery processes of elderly cancer patients

2) Disseminate the useful information

3) Recommend research efforts in selected areas where knowledge is unavailable or ambiguous, and intervention techniques which merit additional exploration and development.

Four common kinds of cancer--breast, colorectal, prostate, and skin--were addressed in the meeting. The discussion centered on (1) health behavior, illness behavior, and early detection of cancer in the elderly; (2) influence of old age on cancer patients to conventional forms of diagnosis and treatment; (4) balance between the treatment and care priorities; and (5) social, emotional, and economic consequences of cancer for the older person. Prevention topics included nutrition problems concomitant with both the process of aging and the disease condition of cancer, and monitoring and screening issues.

The conference highlighted the vast range of issues that exist in both fields of cancer and aging. Current patterns of care for elderly cancer patients were discussed. A dearth of data on the clinical interface of cancer and aging was noted. The jointly-sponsored conference served to (1) bring together a great deal of information which is continually being generated in both geriatric medicine and oncology and (2) identify the research gaps (e.g., in epidemiological studies, in clinical trials; on tumor behavior as related to age; on pharmacokinetics and pharmacology, etc.). The conference proceedings will be available in early 1983.

II.

PREVENTION PROGRAM

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PREVENTIVE MEDICINE BRANCH

The prevention area focuses on primary cancer prevention, cancer screening which utilizes techniques known to be safe, effective, and ready for demonstration and implementation in the community, and applied research in cancer prevention. The primary prevention activities emphasize efforts on populations at risk to cancer due to exposure to carcinogens in the workplace, lifestyle habits, genetic and familial background and general environmental exposures. Studies are also included on screening, cancer diagnosis, refinement of diagnostic guidelines, and the promotion of improved approaches and techniques.

Primary Prevention

Radiation Quality Assurance and Risk Reduction Program

The use of radiation in medicine is recognized as the largest man-made component of radiation exposure to the United States population. Diagnostic radiologic procedures have continually become more varied and useful in medical practice. Radiation therapy has become a recognized modality for the treatment of cancer. Greater than half of all cancer patients will receive radiotherapy at some time in the course of treatment. The emphasis of the Preventive Medicine Branch has been not only on improvements in these diagnostic and therapeutic technologies, but also attention has been devoted to protection and on avoidance of unnecessary and, therefore, undesired radiation.

The Regional Centers for Radiological Physics (CRP), provide quality assurance and risk reduction activities in therapy as well as diagnostic radiology. The CRP's review physics support at all facilities in the DRCCA affiliated clinical programs, and serve as a resource for quality assurance, technology transfer, and education of the radiological community.

The CRP coordination program, conducted by the American Association of Physicists in Medicine, ensures national uniformity in the nature and quality of activities performed by the consensus development, and evaluates the impact of the centers on the cancer control effort.

As of February 1982, the CRP's have carried out 862 reviews of 500 different radiation generators at 344 different facilities. These include reviews of 441 cobalt machines, 409 accelerators, and 12 betatrons. The current number of radiotherapy facilities at which the CRP's carry out reviews is 260. The percent of facilities meeting the 5% tumor dose delivery criteria on the first review was 78%; at the time of the second review, 89% met the criteria.

The CRP's continue to interact with the presently funded DRCCA projects. They are beginning to implement reviews of clinical facilities associated with the Community Hospital Oncology Projects (CHOPS). With the implementation of the Community Clinical Oncology Program (CCOP) and the expansion of the affiliates of the Clinical Cooperative Groups, it can be anticipated that between 100-200 additional facilities will be added to the review program during the coming fiscal year.

The CRP's continue to measure mammographic exposures at 11 mammographic centers under the Community Based Cancer Control Program and CHOPS. Three CRP's have helped review fluoroscopy techniques in the screening of colorectal cancer. A protocol for performance evaluation of computerized tomography equipment has been developed and a pilot survey of 36 facilities conducted. A pilot survey of chest radiography equipment was also initiated in June.

Under an interagency agreement with the Food and Drug Administration (Bureau of Radiological Health) the CRP's have performed a field study of the effectiveness of mammography phantoms on various x-ray units. Physical parameters and phantom images were evaluated from 36 units. The finding of this study suggests that the "random" phantom had advantages over others available for film screen systems.

The CRP's participated in and/or conducted 12 workshops in their regions during the past year. Among the topics considered were radiotherapy safety, thermoluminescent dosimetry, digital radiography, advances in medical imaging, quality assurance in diagnostic radiology, calibration of brachytherapy sources, and treatment planning in radiotherapy.

The agreement with the Bureau of Radiological Health provides for conduct and support of activities that will result in reducing unnecessary radiation to patients and improving image quality by better diagnosis. The BRH continues to provide assistance to states in the mammography program known as Breast Exposure: Nationwide Trends (BENT). To date, approximately 3500 mammography units have been surveyed. This represents more than 80% of the units in the United States. Comparison of data from the initial evaluation and the re-evaluation demonstrates a 27 percent reduction in average exposure. The American College of Radiology is also producing training material for radiation therapists and a protocol for calibration of electron beam energies has been developed and is presently being evaluated.

During this fiscal year a project was implemented with the National Council on Radiation Protection and Measurements (NCRP) to develop a report on mammography and basic radiation criteria. Much information has accumulated on parameters for optimum utilization of mammography including dose reduction and image quality. This information will be incorporated into a handbook which will be made available to practitioners, physicists and public health professionals.

A study at the Peter Bent Brigham Hospital in Boston, Massachusetts (grant 28847) will determine the feasibility of a restricted set of indications for the upper gastrointestinal series (UGI) and the intravenous pyelogram (IVP). An optimal strategy for clinical use of the UGI and IVP examinations will be designed so as to minimize cost and radiation exposure with the least possible loss of important diagnostic information. A series of forms will be prospectively completed by the referring physician, the examining radiologist, and the research physician in three different health care settings. Data will be accrued for the first two years of the project and analyzed during the third.

The overall objective of the American Health Foundation's Primary Prevention of Cancer in Childhood grant program (25521) is to identify major cancer risk factors in school age populations (fifth graders); to reduce the elevated risk

status and to provide continuous reinforcement of health behavior. The program is currently in its second year. The school curriculum was revised to comply with the requirements of the inner-city district of New York. Biomedical screenings were conducted in the study and control groups. The data were collected and stored for analysis at the conclusion of the program.

Secondary Prevention
Screening

Breast Cancer

Active screening in the Breast Cancer Detection Demonstration Project ended in March of 1981 upon completion of the planned period which provided the opportunity for up to five annual screening visits for approximately 280,000 women. A descriptive paper on the data base generated by that program was published in July 1982. Data correction, validation, and analysis will continue until September of 1983. Several publications are anticipated from the analyses of that data during the next year.

A long-term follow-up was designed, approved in 1978, and implemented in January of 1980 to gather health status information on approximately 65,000 women who had participated in the breast cancer screening program. The follow-up was planned for five years with annual contact by mail and telephone of a population which included 1) 4274 breast cancer cases, 2) 25,072 cases having benign breast disease determined by biopsy or aspiration, 3) 25,169 normal controls matched to the benign cases by age, date of entry in the program, geographic location of the project where screening was done and race, and 4) 9685 women for whom a surgical referral was made by the screening project but biopsy was not performed. Twenty-eight interview projects have been established along with a central Data Management and Analysis Center. The earliest projects established are in their third year and the latest ones established are early in their second year. To date a response rate of 98% has been maintained on interviews. In the fourth year of the follow-up, an extensive analysis will be made to determine if the five-year period of follow-up will be sufficient to obtain optional information from the cohorts. This follow-up will provide an excellent opportunity to determine estimates of risk to breast cancer and provide detailed information on the biology and natural history of breast disease for specific defined groups within a screened population.

A study to determine the predictive value of the Wolfe classification of mammograms is in its third year. Preliminary reports indicate that reliability, validity, consistency, and reproducibility can be achieved among radiologists to classify mammograms into the various patterns. An atlas of Wolfe's classification patterns has also been developed. Continuation of the study would seek to apply this training among community radiologists and to explore a possible relationship between estrogen use and the presence of calcifications in mammograms.

To implement part of the cancer control program by demonstrating for the public and medical practitioners the value of earlier detection to decrease cancer morbidity and mortality, a contract with Vanderbilt University, Establishment and Operation of the Pathology Control System for the Breast Cancer Detection and Demonstration Project (PQCS and BCDDP), was awarded for

five years (06/30/76-08/31/81). That contract has been extended for one year for the sole purpose of maintaining a repository of slides as a study resource. The pathology review program began three years later than screenings for the BCDDP. The basic objective was to provide hierarchical review and standardization of procedures, criteria and terminology of the diagnoses of lesions which were biopsied or excised to validate the BCDDP detection process, to permit comparability and analyses of results among projects.

Of 19,036 cases reviewed during the period of active screening, which ended in March, 1981, and submitted for central review to the PQCS principal investigator, 16,189 were reaffirmed as benign, 2,775 as carcinoma (533 in situ and 2,242 invasive), and 72 cases were incomplete when the review contract ended.

Colorectal Cancer

The National Polyp Study, supported by grant 26852 is a project to determine the benefits, risks and costs of a surveillance program for patients who have had polyps removed. Based on seven study groups coordinated by the Memorial Sloan-Kettering Cancer Center, the overall objectives are to determine the best method and interval of follow-up for patients who have had polypectomy utilizing a randomized design. The results of examination by barium enema air contrast x-rays (pneumocolon) and colonoscopy will be compared. The role of the fecal occult blood test will also be evaluated. The overall benefit, costs and risks in the two modality arms of the study will be compared. In the present state-of-the-art, medical practice varies in the recommendation of frequency and method of follow-up examination. This study will attempt to answer the following questions:

1. Should an annual examination be performed routinely after polypectomy or should it be done every three years?
2. Should both one and three-year searches be done?
3. If either x-ray or endoscopy is to be performed as the primary follow-up examination method, which should it be, or should both be done at each contact?
4. What is the value of the fecal occult blood test on an interval examination?

In addition to recommendations on the best methods of follow-up, data will be gathered prospectively on the natural history of adenomatous polyps. The natural history will be correlated with age, family history, and number and histology of adenomas. Detailed uniform pathology is being obtained on all adenomas. Patients have been enrolled in this study for approximately one year. One of the most significant problems has been an unexpectedly low enrollment level to date. Methods of increasing the enrollment are being addressed in the seven study groups.

Before mass screening programs using stool occult blood testing are initiated, improved survival rates in screened individuals should be demonstrated. More information is also needed about the net margin of benefit to health in comparison with the costs and risks entailed in the further study of positive occult blood reactions by barium enema and endoscopy. Many of these screened individuals are found to have benign polyps in the colon.

A major controlled clinical research trial to evaluate survival rates in screened individuals using occult blood testing is being conducted in a study group as a part of the patient examination at the Preventive Medicine Institute Strang Clinic in collaboration with the Memorial Sloan-Kettering Cancer Center. Supported by grant 15529 this project was initiated in the organ site program before the initiation of the cancer control program. Since the primary thrust is to demonstrate the feasibility of screening, it has been transferred to the Preventive Medicine Branch. A detailed description of accomplishments under this grant can be found in the description of the organ site program.

Gynecologic Cancer

The program for gynecologic cancer has supported projects for the study of cervical and endometrial cancers, cancers related to trophoblastic disease, and cancer associated with in utero diethylstilbestrol (DES) exposure. The largest of the above studies was the State/Territorial Health Department Cervical Cancer Screening Program (CCSP). The next largest effort were the studies on the anomalies found in females exposed to DES in utero. Next in order was the trophoblastic disease program in which the goal was to enhance the availability of quality care for women with malignant trophoblastic disease in two regions of assessment of various techniques and the efficacy in detecting endometrial cancers and precursors in asymptomatic women.

The outcomes of the above studies have been varied in terms of definitive answers and quantitative findings. The study for the assessment of techniques for detecting endometrial cancer provided data which recommended endometrial aspiration as a method of choice. It also provided answers on the most effective fixative(s) for the collected tissue samples. The trophoblastic disease programs have provided tangible services to physicians in two U.S. regions in the form of hormone assays for the monitoring of patients with trophoblastic disease. The laboratory studies also undertook the identification of unique macromolecules whose presence might serve as predictive markers. The positive impact has been based on the willingness of the local physicians to avail themselves of the clinical and laboratory expertise provided by the two centers, and their interest in participation as a whole. During the final year of study, more information on the program's effectiveness should become available.

The DES study is directed toward an understanding of the abnormal lesions seen in females who were exposed to the hormone in utero. Four study centers, the Baylor College of Medicine, The Massachusetts General Hospital, the Mayo Foundation, and the University of Southern California have collected data on more than 5000 women through yearly physical examinations. Two publications describe the major findings as vaginal epithelial changes and other pathologic lesions. The first paper dealt mainly with the frequency and duration of vaginal lesions. The second major paper discussed the pathologic findings which ranged from adenosis to clear-cell cancer based on a survey of several thousand biopsy specimens. At this time in the analysis, the relation of adenosis to clear-cell cancer remains tentative. In the concluding months of the DESAD program, greater emphasis will be given to the analysis of collected data. These analyses might permit more definitive statements about vaginal epithelial changes (adenosis), pathologic findings, and perhaps disease natural history.

The largest effort in the area of gynecologic cancer has been the screening program for cervix cancer. The program will be concluded during July 1982 and will have screened more than 1.2 million women. The design of the study was not constituted for a direct analysis along the lines of prevalence, incidence, and relative risk. Accordingly, an indirect or modeling approach was used with the data in lieu of a more conventional analysis. The computer-assisted model was used to estimate the probability for any given disease state among precursors and invasive cancer.

Grant Programs were supported to study the relationship between endometrial cancer and estrogen replacement therapy in postmenopausal women. One project entitled Cancer in Women Receiving Exogenous Estrogen (29543) by the University of Denver, confirmed that the changes in the cancer incidence rates are inversely related to the rate of estrogen prescriptions. An annotated bibliography was completed and disseminated to obstetricians/gynecologists, family and general practitioners, internists, doctors of osteopathy and general surgeons in the Denver metropolitan area. The other project entitled, The Educational Approaches to Endeometrial Cancer (25280) being performed by the New York State Health Department is a demonstration education program, but includes a retrospective study of the causes of the sharp decline in estrogen prescriptions since 1977, and a population survey of the symptoms of perimenopausal women. The study will be completed in FY 83.

Lung Cancer

A collaborative study involving three institutions, Memorial Sloan-Kettering, Johns Hopkins University, and Mayo Foundation, currently is in progress to evaluate possible effectiveness of diagnostic procedures in early diagnosis, and hence earlier treatment, of lung cancer in males at high risk for developing lung cancer.

The goal of the study is: to test new methods for diagnosis of early lung cancer and to assess survival of patients with lung cancer detected by these methods. The three studies are operated independently but with frequent interchange of information and several meetings per year.

Recruitment for the Memorial Sloan-Kettering Cancer Center National Lung Program was completed in January 1978. Total enrollment is 10,040. Participants were randomly assigned to the Study Group (4,969), receiving annual chest x-rays and 4 monthly sputum exams; and to the Control Group (5,071), receiving annual x-rays only. There have been a total of 188 confirmed lung cancers identified so far, 94 in the Study Group and 94 in the Control Group. The principal mode of detection in the Study Group was by cytology in 19 cases, x-ray in 48 cases and both techniques in 7 cases. Of the 19 cases detected by cytology, 12 were Stage 0 or I; of the 55 cases detected by radiology in the Control Group, a total of 118 cases, there were 57 in Stage I. There were 51 interval cancers diagnosed following symptoms or signs, and 19 were oat cell cancers.

Among the 94 lung cancers appearing in the Study Group, 31 were prevalence cancers for a prevalence rate of 6.2/1000 and 63 were incidence cancers for an incidence rate of 3.0/1000/year. In the Control Group the 94 lung cancers included 22 prevalence for a prevalence rate of 4.3/1000 and 72 incidence cases, for an incidence rate of 3.4/1000/year. Survival rates so far have

been excellent for the cases detected early (Stage 0, I), with 5-year survival estimated at better than 90%.

A total of 10,828 men have been enrolled in the Johns Hopkins project, of which 5,407 were randomized into the Control Group and 5,421 into the Study Group. To date, 609 have died, while 1,316 have withdrawn from the study or moved from the area. Currently, 8,463 remain as active participants; 4,289 in the Control Group and 4,174 in the Study Group. At the initial screening 74 cancers were detected (39 in the Control Group and 35 in the Study Group) for a detected prevalence of 7.1 per 1,000. Following an initial negative screening, a total of 169 cancers have developed (89 in the Control Group and 80 in the Study Group) for an incidence of 4.6 per 1,000. In the Study Group there were 12 cases detected (15%) in Stage 0 and 28 (35%) in Stage I; thirty-three additional cases occurred in that group between screening procedures. In the Control Group no cases were detected in Stage 0 and 33 (37%) were in Stage I; 33 additional cases occurred in the group between screenings. Among the 80 incidence cases detected in the Study Group, 40 (50%) were resected; 40 (45%) of the 89 incidence cases detected in the Control Group were resected. Two hundred forty-three total lung cancers have appeared in the screened population, 128 in the Control Group and 115 in the Study group. Among the 128 cases of lung cancer found in the Control Group 76 (59%) have died; 49 (43%) of the 115 lung cancer cases in the Study Group have died. The observed rates of lung cancer mortality are 42 per 10,000 person-years in the Control Group and 25 per 10,000 person-years in the Study Group.

At the Mayo Foundation both the Study Group and the Control Group have been observed more than 23,000 man-years, and 243 new ("incidence") cases of cancer of the respiratory tract had been detected, 55 involving the upper airway and 188 the lungs. In the Study Group there were 110 new lung cancers (12 of which were detected by cytology only) and 51 lung cancer deaths. Early survival data in this group are encouraging. In the control Group there were 78 new lung cancers and 54 lung cancer deaths. Thus, once lung cancer has been detected, survival in the Study Group appears better than among the Control Group. However, further observation and prolonged follow-up are essential before final conclusions and specific recommendations will be possible. As "incidence" cases continue to accrue, more detailed analyses of data are becoming feasible. Particular attention is currently being directed towards evaluation of the results of screening by cell type of tumor and by modality of detection. The post-surgical American Joint Commission Stage I lung cancer study indicates that 69% of those with no-small cell cancer survive 5 years. The Hematoporphyrin Derivative study has detected several squamous cancers that were both radiographically and endoscopically occult. Cryotherapy continues to be used in selected cases.

Pathology

Under the cancer control technology transfer dimension of continuing professional education, two three-year contracts were awarded on Professional Education in Cytology Related to Bladder, Lung, Colorectal and Cervical Cancer, for the period 09/30/79-09/29/82, one to the University of Washington (#95435) and one to the St. Louis University (#95485), both having experienced cytopathologists as principal investigators (P.I.). The goals of these contracts were to reduce morbidity and mortality from cancer, by helping to assure the widest possible awareness and use of the latest advances in

concepts, knowledge and practical procedures of earlier detection and presumptive diagnosis of cancer using cytology. The goals were emphasized, especially in the more frequent and difficult cancer sites, such as colon/rectum and lung, which are examined by practicing cytopathologists, cytotechnologists and cytology laboratories. Each contractor was expected to provide special continuing education to at least 250 cytotechnologists (CT) and 50 cytopathologists (CP) during the three years; continuing education units or credit hours are given for completing the course.

St. Louis University was the site of several two-week courses and the University of Washington sent workshop teams to cost-effective sites in the Western States, mostly in Washington and Oregon. A Steering Committee consisting of Principal Investigators and the Project Officer met during the contact period to compare curriculum and problems. Although both programs had more difficulties than anticipated with recruitment and retention (30% no-shows), related to shortage of personnel for laboratory coverage during trainee absences, the St. Louis contractor completed 13 courses and the Seattle contractor 25 workshops. Updating of knowledge, new laboratory expertise, test and follow-up materials have been provided to 394 cytotechnologist and 338 cytopathology enrollees. During the past two years Dr. John Berg (grant 31802) has developed and tested computer programs designed to scan newly-acquired cancer registry data and to isolate cancers of specific histological types such as angiosarcoma or those occurring in anatomical subsites such as the pleura that have shown a significant increase in relative frequency. A major part of the work consisted of grouping cancers together that were known to be alike on the basis of past knowledge or simple examinations of the test data. Two problems have emerged which indicate that further work is required. First, the new coding scheme, WHO's International Classification of Disease for Oncology, 1976, (ICD-O), has far more categories than those used in the past. Hence, the identification of synonyms becomes much more important if the analyses are not to be confounded by a plethora of misclassifications for the same entity. Second, and perhaps more important, while the programs are designed to precede but not replace formal calculation of incidence rates, such calculations for specific histologies and for many anatomical subsites appear difficult or impossible with present reparting. Much more must be learned of the special characteristics of patients with unconfirmed cancers and of the cases given only histologic site designations. The continuation of this work is expected to resolve many of the difficulties encountered by the lack of uniformity in coding.

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Letton, A. H. and Mason, E. M.: Five-year plus survival of breast screenees. CANCER, July 15, 1981, 48 No. 2.

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OCCUPATIONAL CANCER BRANCH

The Occupational Cancer Branch (OCB) was established in July 1980 to create a focus at the NCI for applied research and other activities aimed at prevention and control of occupational cancer.

At the time of its formation, the Branch was given responsibility for several occupational cancer programs begun under other auspices. These consisted mainly of efforts to inform or educate workers about the risks of occupational cancer and to organize community support for medical surveillance and follow-up for workers known to be at high risk of occupational cancer or who had experienced an apparently increased incidence of cancers of certain sites suspected to be of occupational origin.

Planning in Occupational Cancer

The Branch has devoted most of its efforts during the current year to a systematic review of the problems of occupational cancer, with a view to drawing up a program designed to produce demonstrable benefits (in terms of reduced risk of exposure or disease) for workers whose occupations put them at elevated risk of cancer.

These efforts suffered a significant handicap with the untimely death in December 1981 of the Acting Branch Chief, Dr. Margaret H. Sloan, and the later death of Dr. Andrew Hegyeli in June 1982.

The staff has been assisted in its planning by an advisory committee of the DRCCA Board of Scientific Counselors. The result of these deliberations, to date, is that a general framework for a program has been worked out. The principal elements of the plan include support for efforts to identify, monitor, and control occupational cancer risks in defined groups; to intervene to prevent occupational cancer through education and training; and to monitor progress in efforts to reduce the risk of occupational cancer. In order to centralize the currently fragmented basic information on occupational cancer and to provide a clearinghouse and source of data for research workers, it is also proposed that the idea of establishing a data center for occupational cancer be considered. Such a data center would, of course, require the collaboration of the many other agencies and organizations with interests in the field.

Community Based Occupational Cancer Intervention Program

The Western Institute for Occupational and Environmental Sciences (WIOES) has been supported by contract (95450) to establish the Bay Area Asbestos Awareness Project. The main objective of this project is to inform workers, their families and the public about the hazards of exposure to asbestos and other occupational and environmental carcinogens.

The Workers Institute for Safety and Health (WISH), through a grant (27582) is supporting community-based cancer intervention programs at the Ford and General Motors companies for 15,000 pattern-makers believed to be at high risk of developing colon/rectal cancer. The etiological agents are not known, but the higher rate of cancer observed by NIOSH in these groups might be associated with exposure to wood dust, solvents, adhesives and other chemicals. Medical surveillance for these groups is provided by the employers. A similar program was established by WISH for about 1,000 workers in Augusta, Georgia, known to have been exposed to beta-naphthylamine. The medical follow-up for this group is conducted in collaboration with NIOSH, and the medical surveillance of the workers is provided by the Medical College of Georgia. A third group followed under this grant is an asbestos-exposed cohort of about 12,000 workers in Port Allegany, Pennsylvania. The medical surveillance in this group is paid for by the company and is conducted in collaboration with the Mt. Sinai School of Medicine in New York.

Education of Workers

Through an Interagency Agreement with the Occupational Safety and Health Administration (OSHA), the Branch has supported cancer-related portions of the Institutional Competency Building Program (New Directions) grants for the education and training of workers about occupational health hazards. As a consequence of the decentralization of the management and evaluation of these grants by OSHA, the Branch has been exploring methods by which the cancer-related New Directions grants could be brought under direct NCI administration. The concept of continued support of these grants, with direct review and management by NCI, was approved by the DRCCA Board of Scientific Counselors. The staff has issued a request for grant applications (RFA) to provide the means for funding and to ensure appropriate peer review.

The Resource Center of WIOES (95450) published a "Workers Guide to Radiation" and developed fact sheets on health hazards in shipyards and in the electroplating industry. The "Asbestos Newsline," a semiannual news letter, and an article entitled "Legal and Ethical Dilemmas of Worker Notification," edited by F. S. Lee and W. N. Room, Legal and Ethical Dilemmas in Occupational Health, Ann Arbor Science, 1982, provided much needed information to the public.

Under the grant entitled Environmental Cancer Prevention and Labor Health Education (27557) the Johns Hopkins University, in collaboration with the Center for Labor Studies in New York, has developed and field tested several model occupational cancer health education programs. The final version of the cancer education curriculum for workers is being prepared for field test and evaluation.

Education of Health Professionals

The Resource Center of the Bay Area Asbestos Awareness project 95450) conducted 21 professional education workshops for physicians and other health care providers on asbestos and other occupational cancer agents. A forum was held for health professionals, and the staff members of the Speakers Bureau provided speakers for

professional and community information programs on the harmful effects of asbestos and other carcinogens. The Center cosponsored the continuing education conference, "Hidden Health Hazards in the Environment." WIOES developed the course material and served as faculty.

A National Correspondence Course on Lung Cancer and Asbestos-Related Pulmonary Disease, by the American College of Chest Physicians (95455), was completed and published. To date, about 40,000 copies have been distributed to physicians specializing in pulmonary diseases, occupational medicine and internal medicine, and for use in medical schools, cancer centers and special training courses. This course, which is based on intensive review of the world literature, is believed to be unique in its field and has been very well received.

Staff Publications

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Hegyeli, A. F.: The Use of Cell Cultures for Biomaterials Testing. In Nardon, R. M. (Ed.): Toxicity Testing In Vitro. New York, Academic Press, 1982 (in press).

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BEHAVIORAL MEDICINE BRANCH

The Behavioral Medicine Branch has responsibility for planning, conducting, and directing a program of biobehavioral research related to cancer prevention, early detection, and treatment. The scope of current research programs extends from health promotion/disease prevention issues through behavioral contributions to the course and treatment of cancer and its aftermath to the broader social impact of the disease (Cullen, Fox, and Isom, 1976; Levy, in press). The ultimate aim for research across all of these areas is the translation of study findings into community practice in order to control cancer in the population at large.

The table below displays FY 1982 expenditures for behavioral medicine extramural research across these three program areas.

Fiscal Year 1982 Funds by
Extramural Program Area Within the

Behavioral Medicine Branch
(Dollars in Thousands)

	Primary Prevention	Secondary Prevention	Treatment
Grants	1,249	659	1,886
Contracts	500	---	90
TOTAL	1,749	659	1,976
GRAND TOTAL		4,384	

Extramural Programs

Primary Prevention Research

Research within this category is concerned with health promotion/disease prevention efforts, including identifying environmental and developmental factors associated with at-risk status for the future development of cancer, as well as altering unhealthy lifestyles (for example, smoking or excessive alcohol consumption in order to prevent the carcinogenic effects of known risk factors. This is a major program area targeted for future growth; current funded projects involve the estimation of environmental and behavioral contributions to morbidity and mortality (28163 and Y01-CN-00711), the identification of early childhood experience contributing to future cancer risk (24416), and a number of research activities in smoking prevention and cessation. This latter program area is of particular importance to the Institute as well as this Division, and more will be said below about future program plans in this area.

The Behavioral Medicine Branch supports research aimed at understanding the nature of bio-behavioral dependence on smoking and tobacco use and its

development in high-risk subgroups that are not decreasing usage (e.g., adolescents, females, minorities and workers exposed to known or suspected carcinogens). Special attention has been given to evaluation of smoking prevention and cessation interventions with a special emphasis on self-help techniques.

Projects supported by the BMB have contributed to a nationwide effort to reduce the incidence of cancer and related morbidity and mortality due to cigarette smoking and tobacco use. Data concerning bio-behavioral antecedents and correlates in subgroups (29558 - Smoking Prevention in Youth, 29640 - and Smoking Prevention Training for Youth, 30237 - Adolescent Antecedents of Cigarette Smoking Behavior in Special At-Risk Populations); endocrine functioning and central nervous system correlates (29231 - Environment, "Need for Stimulation", and Smoking , 29320 - Gonadal, Behavioral and EEG Correlates of Smoking); and identification of factors which may assist the "resistant" smoker (27821 & 29479 - Informal Self-Help Approaches to Smoking Cessation, 27092 - Factors in Self-Help Smoking Cessation Attempts, 27332 - The Self-Help Process in Smoking Cessation) are to be translated into prevention and cessation strategies with the aim of reducing cigarette smoking and tobacco use. There is suggestive evidence that application of these strategies is likely to have the impact of reducing cancer related mortality through a decline in incidence rates.

Secondary Prevention Research

D'Onofrio (1982) described two major purposes of behavioral research related to cancer screening and early detection. One purpose is to advance the effective application of currently approved screening methods (e.g., pap test or mammography for women over 50), as well as to identify factors associated with non-compliance which could then expedite the application of other screening methods as these become perfected. The second purpose of behavioral research related to early detection of cancer is to contribute to the evaluation of screening tests on the technical criteria of yield, cost, and acceptability. Recent research has shown that there are still population subgroups (e.g., the socially and economically disadvantaged) that underutilize screening and detection tests, and fail to follow through with early diagnostic referrals (Berg, J, Ross, R., and LaTourette, N., 1977; Devesa and Diamond, 1980). Future research and demonstration efforts should be aimed at recruiting such subgroups into cancer detection and early treatment activities. There are two major categories of secondary prevention research currently being supported within the Branch program area: Health behavior related to health care utilization and the practice of breast self-exam (BSE) as a patient-oriented cancer detection strategy. As an example of research within the first category, Francis (27281) is examining factors related to delay in diagnosis--symptom, patient, physician, and health care system characteristics--as well as to examine access, continuity, and satisfaction with care received.

Breast Self Exam (BSE) is a particularly unique detection activity, in that it relies wholely upon the behavioral initiation and accomplishment of the lay person, herself. In this sense, it is a "patient-centric technology" (Levy, and Howard, in press). Although still under investigation, the weight of the evidence suggests that BSE may facilitate the earlier diagnosis of breast cancer and thereby reduce morbidity and mortality from this disease. The Behavioral Medicine Branch supports research efforts relevant to testing the screening value of BSE (26363), as well as the utilization of the technique (18451, 28269, and 26216). In Foster's (26363) study, data are being collected in the state

of Vermont to determine the relationship between BSE performance, the clinical and pathologic stages of breast cancer at diagnosis, and survival outcome. In this study, a retrospective analysis of tumor registry data through 1979 revealed a significant association between increased frequency of BSE performance and more favorable (TNM) clinical stage of disease at diagnosis. This investigator is currently continuing with a prospective study, examining women who were taught BSE during implementation of a breast cancer network demonstration project in Vermont, and were subsequently (1979-1984) diagnosed with breast cancer. These investigators will then examine whether trends found in the retrospective data favoring women who practice BSE frequently will hold up in the prospective data. They will also attempt to analyze survival curves for women diagnosed between 1975-1979, to see if BSE performance is related to decreased mortality.

The Branch is also reviewing the spectrum of research evidence related to the efficacy of BSE as a detection strategy, and this activity will be discussed below.

Treatment and Continuing Care Research

The treatment and continuing care projects can be grouped into those related to the behavioral management of adult cancer patients, those related to symptom control, and those related to disease and treatment sequelae in pediatric populations. Since behavioral medicine is an interdisciplinary research approach to understanding disease processes, research in the treatment area is not (or should not be) primarily concerned with mental health or behavioral dysfunction variables as ends in themselves. These factors are important only as they influence the course of the disease, its symptomatic expression, or its outcome. This effect can be direct (for example, stress effects on hormonally dependent tumors) or indirect (for example, non-compliance compromising treatment effectiveness). Although not all of the treatment projects currently supported within the BMB directly address the course of the disease and its associated symptoms, ultimately these are the fundamental questions that should be pursued. During Fiscal Year 1982, there were 20 treatment and continuing care projects supported. Only a sample of these will be discussed here.

The Psychosocial Collaborative Group (PSYCOG, 19681) is in its sixth year of investigation into the nature and frequency of emotional and behavioral sequelae in patients receiving chemotherapy and/or radiation therapy. This consortium of investigators from Memorial Sloan-Kettering Cancer Center, The Johns Hopkins Medical Center, and the University of Rochester Medical Center has also examined such issues as the process of informed consent to investigational protocols and the effectiveness of certain psychopharmacological interventions in the amelioration of pain and distress. A recently completed study by PSYCOG revealed significant undertreated levels of clinical depression among cancer patients. PSYCOG is currently initiating a clinical trial, examining the efficacy of a tricyclic antidepressant (nortriptyline) in the amelioration of depression and pain.

There are three additional studies supported through the BMB. They are related to the control of emotional distress and adverse side-effects in chemotherapy patients (26235, 25516, and 26832). Preliminary findings from one of these studies indicated that a behavioral intervention (systematic desensitization) produced a significantly greater reduction in anticipatory side-effects than either counseling or non-intervention. If these findings are reliable, these behavioral techniques could be valuable for symptom control in community settings.

A research program that spans detection, diagnosis, and treatment activities relates to patient compliance. An RFA entitled "Cancer Patient Compliance with Therapeutic Regimens" was released in FY 80. Three R01 grants have been funded: two of them (31151 and 31157) concerned with compliance and toxicity in adult chemotherapy patients, and the third (31167) concerned with dental compliance in head and neck patients receiving curative doses of radiotherapy. Findings from these studies should enable those treating cancer patients to predict subgroups at risk for non-compliance, and to intervene in order to achieve optimal treatment outcome.

In the pediatric area, there are three behavioral projects (26292, 27376, and 33340) related to the management of pain and distress in children with cancer. Kellerman's (26292) and Zeltzer's (27376) work have utilized hypnosis and the training of self-hypnosis in children undergoing bone marrow aspiration and chemotherapy, supporting the effectiveness of hypnosis as an intervention to reduce anxiety and discomfort for adolescents undergoing chemotherapy.

In general, the cognitive, behavioral, and emotional sequelae of disease and its treatment in long surviving pediatric patients is an important area of investigation in secondary prevention. That is, these children may be at risk not only for recurrence of disease, but also for developmental defects arising directly from the treatment of their primary disease.

BMB Staff Collaboration

In addition to scientific program areas within the Branch, branch staff--because of particular expertise in the behavioral sciences--also consult and collaborate with other branches in the Division. An example is staff collaboration in the development of chemoprevention trials, where questions of behavioral compliance related to "drop-ins" and "drop-outs," and issues concerned with trial ethics must be considered in sample size calculations and trial methods development.

Staff Research

Emotional Response to Breast Cancer and its Treatment: NCI Protocol No. 80-C-49 (Dr. Sandra M. Levy)

There have been studies in the U.S. and England with breast cancer patients suggesting a link between emotional expression, "fighting spirit", and better disease outcome. The objective of this study is to investigate whether outward emotional expression, as compared to passivity, is significantly associated with an increased survival in metastatic breast cancer patients. Cognitive and behavioral components of the patient's response to her illness are being analyzed to identify responses associated with better disease outcome. Preliminary findings showed that when the first 22 patients were divided at one-year follow-up into three groups of stable, progressing, or dead, the stable group had expressed significantly more emotional distress at baseline than the other two groups ($P<.05$). This psychological response appeared to be independent of any biological difference between the outcome groups at baseline testing.

If the association between emotionality and survival is reliable, an intervention study will be developed to attempt to build in a psychological response of the character found to be associated with survival in this present work. A second aim will be to measure biological correlates of these response patterns.

Breast Cancer Diagnosis in Minority Groups (Dr. Jan Howard)

A collaborative investigation with the staff of the Epidemiology Branch (DCCP) is in progress to examine the interactive effects of race, socioeconomic status, age, and marital status on the stage of breast cancer at diagnosis in 22,000 female cases recorded by the California Tumor Registry. Dr. Howard has also reviewed the health care literature relevant to the unequal burden of cancer endured by certain disadvantaged groups in American society, such as the poor and blacks (see below).

Breast Cancer Laterality: Effects on Survival (Dr. Jan Howard)

In cooperation with scientists in the Biometry Branch of DCCP, the investigator is exploring the relationship between the side of female breast cancer and relative survival rates at 5 to 10 years after diagnosis. Several stratification criteria are being utilized: stage of disease at diagnosis (localized, regional, and remote); age (younger and older than 55 years); and data source (End Results data from 1967 forward and Seer data from 1973 forward). Relationships between laterality and stage of disease are also being investigated. A published paper from Israel showed no association between laterality and survival over a 15-year period, but preliminary findings from the NCI study suggest that women with cancer of the left breast may have a poorer prognosis than those with cancer of the right breast.

Health Beliefs Related to Cancer in Minority Subgroups: A Pilot Study (Dr. John Friedl)

A descriptive pilot study is underway in Washington, D.C., with the aim of developing a survey instrument that can then be applied to a larger population sample. The objective of the survey is to describe and analyze health beliefs associated with early diagnosis and treatment of cancer in Hispanics and black population subgroups.

Scientific Seminars and Working Groups

The BMB has sponsored one scientific working group related to BSE, and three seminars related to the topic of smoking and cancer. A fourth seminar was co-sponsored with the NIH Working Group on Health and Behavior relating to health beliefs and health care utilization.

Future Plans and Projects

Future program areas are in various stages of development. These range from primary prevention through rehabilitation and terminal care. Emphasis, however, will be placed on primary and secondary prevention issues.

Primary prevention areas of major importance to the Branch will be concerned with the alteration of lifestyle factors associated with cancer risk. These include investigations into the nature of nicotine dependence, its development as well as its cessation; the modification of nutritional intake as epidemiological evidence suggests a link between diet and cancer risk; and the modification of other forms of addictive behavior such as excessive alcohol consumption in population subgroups. In addition, the alteration of the behavior of those exposed to other environmental carcinogens (such as those found in the workplace), and the development of effective risk counseling techniques are areas of future program interest.

Two specific initiatives in the area of tobacco use and cancer risk have recently been initiated in the form of Program Announcements. One of these is concerned with the prevention and cessation of smoking in blue collar workers; the other is concerned with behavioral, epidemiological and biobehavioral studies related to the use of smokeless tobacco in adolescents. The latter practice has been found to be associated with a higher incidence of oral cancer in population subgroups, and current media efforts aimed at recruitment of the young to smokeless tobacco use makes this an area of programmatic concern to the Institute and the Division. It is hoped that research responding to these two initiatives will ultimately lead to reduction in lung and oral cancer in the U.S. population.

In terms of secondary prevention program areas, the major focus of concern will be on what has been referred to as "patient-centric technologies" (Levy and Howard, 1981). That is, the Behavioral Medicine Program will be particularly concerned with understanding and fostering patient-initiated behaviors in the area of screening and early detection. An important future program area will be the health beliefs/behavior of the disadvantaged in order to isolate factors that can be modified, thus improving prognosis in these subgroups. Along these lines, an RFP in the area of black/white differences in treatment outcome is being initiated by the BMB, DRCCA, in collaboration with scientists in DCCP. The aim of research supported under this funding mechanism will be to isolate factors that significantly contribute to differential survival between blacks and whites in the U.S., including genetic, histological, immunological, and behavioral contributors to outcome.

Program priorities in the area of treatment and continuing care will involve the application of behavioral techniques that lend themselves to systematic, quantifiable research on problems associated with cancer patient care (pain control, nutritional deficits, anticipatory nausea and vomiting, etc.). And certainly the area of terminal care (particularly in pediatric patients), including the systematic analysis of environmental variables affecting the course and nature of dying, remains an important area for future work.

Across all of the above program areas, fundamental research needs to be carried out concerned with the biological correlates of behavioral patterns--from smoking initiation to non-compliance with chemotherapy. In addition, the fundamental search for mediating mechanisms between behavior and disease needs to be pursued at every level. And ultimately, this new knowledge must be generalized and applied to population subgroups at risk in order to achieve reduction in cancer incidence, morbidity, and mortality in the population at large.

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III.

CENTERS AND COMMUNITY ONCOLOGY PROGRAM *

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TREATMENT, CONTINUING CARE, AND REHABILITATION PROGRAM

Program Scope and Strategies

The activities supported by the Treatment, Continuing Care, and Rehabilitation Program focus on applying successful research advances and practical cancer control interventions in the community. By implementing proven technology and successful methods of cancer patient management in various settings, increasing the involvement of community health care professionals in cancer care, and facilitating the dissemination of the vast therapeutic experience in cancer control, this program attempts to reduce the impact and effects of cancer for the nation's population.

The Treatment, Continuing Care, and Rehabilitation Program addresses extramural research programmatic efforts under four organizational components which include the: (1) Community Outreach and Rehabilitation Branch; (2) Cancer Centers Branch; (3) Organ Site Branch; and (4) Research Facilities Branch. Each Branch emphasizes and develops programs which foster multidisciplinary cancer management at the community level and encourages the demonstration of effective application of successful approaches in cancer control.

A primary emphasis in this past year has been on establishing a large-scale cancer control effort involving practicing community oncologists in NCI clinical trials programs. This program initiative, known as the Community Clinical Oncology Proogram (CCOP), is discussed under the Community Outreach and Rehabilitation Branch Program. Community physicians will work with regional cancer centers and/or national cooperative cancer research groups to place cancer Patients on protocol protocol studies. Another recently initiated long-range program, Cancer Control Research Units for Defined Population Studies, is discussed under the Cancer Centers Branch section. This new programmatic effort will support specialized research units to conduct studies on the impact of cancer control activities on the incidence, morbidity, and/or mortality of the general population.

The Treatment, Continuing Care, and Rehabilitation Program is the NCI focal point for several areas of special interest in Cancer Control. Among the more prominent research and demonstration activities supported are (1) rehabilitation, both physical and psychosocial; (2) pain control; (3) improved approaches to the care of patients with advanced cancer and the support of their families; (4) organizational research, and (5) studies of the education, attitudes, and behavior of physicians, nurses, and other health professionals. The investigations are designed to address cancer control issues relevant to patients, families, the public in general, volunteers providing care, health professionals, and those persons organizing to deliver cancer care.

Cancer control projects which come under the Treatment, Continuing Care, and Rehabilitation Program will continue to emphasize (1) participation of physicians in the community who are experienced oncologists to reduce the time that important advances in treatment research may be applied to cancer patients in the community; (2) interhospital relationships linking community hospitals with cancer center resources; and (3) support of efforts to expand and extend the cancer care knowledge base. As a new thrust, the program is encouraging cancer control research which develops or tests actions or interventions aimed at specific high risk population groups. It is also anticipated that new directions will include examining the social, economic,

and emotional burdens which cancer creates for patients and families. Relationships shift with the reordering of priorities of daily living. Rigorous study of areas of beneficial manipulation is needed. Single and combinations of interventions to reduce or eliminate these burdens represent fertile areas for future exploration. Branch activities currently being conducted follow.

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CANCER CENTERS BRANCH

Since the early 1960's, the National Cancer Institute (NCI) has conducted a Cancer Centers Program to provide grants for the support of programs in cancer research, education, and cancer control at educational and research institutions in the United States.

The primary objective of the Cancer Centers Branch is to promote and support the development of both specialized and multidisciplinary programs in laboratory and clinical cancer research and applied research in prevention and treatment.

This description of the Cancer Centers Branch will focus upon the principal instruments that serve its primary objective: Cancer Centers Support (Core) Grants, the Centralized Cancer Patient Data System, and the Cancer Control Outreach Program.

Cancer Centers

Purpose

The principal purpose of cancer centers is to extend knowledge and understanding of the causes, mechanisms, diagnosis, and treatment of the multiple forms of cancer through the development of either specialized or broad multidisciplinary programs in basic and clinical cancer research.

The rationale for centers is that the increasingly complex and costly demands of modern cancer research can be effectively and efficiently advanced by creating environments conducive to interdisciplinary coordination and collaboration.

General Characteristics

Cancer centers are unique and flexible entities and are not patterned after rigid models. They have developed from areas of existing strength to encompass a variety of activities ranging from highly specialized and narrowly focused programs to broad, coordinated, multifaceted programs. Cancer centers provide a national resource for the conduct of the full spectrum of activities necessary to achieve the objectives of the National Cancer Program.

As a national resource, cancer centers provide a critical core of: (1) highly trained laboratory and clinical research personnel; (2) physical facilities and equipment; and (3) administrative support structures. These three elements facilitate the generation of new knowledge about cancer and accelerate transfer of new information about cancer prevention, diagnosis, treatment, rehabilitation, and continuing care to health professionals in their surrounding communities and to the general public.

Types of Cancer Centers

Cancer centers have developed in a number of different organizational settings. Some are independent, free-standing institutional entities; others are under the auspices of universities; still others are consortia or multi-institutional in nature. Although any cancer center needs a certain minimum number of research programs for a "critical mass," centers vary greatly in size and breadth of programs from rather small specialized centers to large complex comprehensive centers. They may be classified as follows: (1) Laboratory Cancer Research Centers (LCRC)--centers engaged only in laboratory research; and (2) Clinical Cancer Research Centers (CCRC)--centers engaged in both laboratory and clinical research.

In addition, a Clinical Cancer Research Center (CCRC) with a funded Cancer Center Support (Core) Grant may apply to the National Cancer Institute for recognition as a Comprehensive Cancer Center. Such recognition may be granted by the Director of the National Cancer Institute if evaluation of the center demonstrates compliance with the guidelines for comprehensiveness established by the National Cancer Advisory Board and revised by the Board in 1979.

In FY 1982, a total of 62 cancer centers had active core grants, of which 16 are Laboratory Cancer Research Centers. Of the remaining 46 centers which are either clinical centers or which combine both basic and clinical research programs, 20 have been designated as Comprehensive Cancer Centers. Appendix I lists centers by type.

National Cancer Institute Support for Cancer Centers

Although cancer centers' activities are funded by both Federal and non-Federal funds, more than 66 percent of their total financial support is drawn from the NCI. An important funding mechanism is the Cancer Center Support (Core) Grant (CCSG) available through the Cancer Centers Branch, NCI. All types of cancer centers are eligible for a core grant. Applications undergo competitive scientific and technical review according to the prescribed peer-review procedure of the NIH.

The purpose of a CCSG is to provide a mechanism for support of those elements of a cancer center required for the planning, development, evaluation, administration, and maintenance of an active and unified cancer center in order to consolidate and focus cancer-related activities in a single administrative and programmatic structure. The CCSG may support salaries for key professional and administrative personnel, shared equipment, special facilities and services, alteration and renovation, and developmental research activities. A unique and important feature of the core grant is its provision of funds for major equipment and shared resources and services for which funds would not be possible or appropriate from individual grants or other grant programs. By virtue of being shared, such resources may result in a cost saving to the center and, therefore, to the National Cancer Program. Specific examples of shared resources include media preparation, glassware washing, animal colony central services, clinical research bed units, etc. For these shared resources and services, only costs for centralized services may be charged to the CCSG. Costs directly related to individual research projects must be charged to the applicable project.

It is important to emphasize that research itself is not supported by the core grant except for developmental projects. Despite its importance, the core grant provides only a minor portion of total support for the centers. Recent analyses have shown that core grants account for an average of 12 to 13 percent of total cancer center funds. The major portion of cancer center research is funded by combinations of individual research grants, clinical and basic program project grants, cancer control grants, clinical education and training grants, fellowships, contracts, and various funds received by the centers themselves from other Federal, non-Federal, and local sources. As a support structure for laboratory and clinical cancer research, the core grant makes no provision for funding cancer control or education and training activities. These important cancer-related activities are eligible for funds from other NCI sources.

Core Grant Awards

Decisions concerning final approval and award of funds are based upon review recommendations, priority scores, and the availability of funds. Continued support through this mechanism requires submission of a renewal application which is reviewed in the same sequence of steps as an initial application.

If a cancer center's renewal application is disapproved or fails to achieve a priority score which permits funding, the center enters a "phase-out" period during which it may receive a specified fraction of its current funding level for up to 1 year after initiation of the action. During this interim period, centers may resubmit a competitive renewal application. Loss of a CCSG grant by a comprehensive center automatically requires re-evaluation of the comprehensive designation.

The Growth of Centers—Consequences and Implications

Enactment of the National Cancer Act of 1971 marked the beginning of a period of rapid growth of the Cancer Centers Program. In addition to an increased number of centers, there has been a concomitant growth in their size and complexity, expansion of their research programs and activities, and augmentation of their professional staffs. These elements of growth coupled with the rising costs of research have been reflected in steadily mounting financial needs and requests.

Cancer centers depend heavily upon the NCI for research and operational support funds. The NCI contributes an average of 66 percent of total external support funds; other NIH programs provide an additional 20 percent. The total NIH contribution is, therefore, 86 percent of all external financial support. The remaining 14 percent derives from other Federal, public, and private sources. Any changes in the NCI budget appropriation and its apportionment can be expected to have a significant impact upon the research and operational stability of the cancer centers.

Current Problems

With the recent leveling of NCI and NIH appropriations, centers' rising costs have become a source of concern for both centers and the NCI. The limited growth of the NCI and NIH budgets have made research grants increasingly competitive and less certain as sources of funds for investigators. As a result, the core grant support program has received increased attention. Although the core grant constitutes an average of 12 to 13 percent of total cancer center funds, it is a critically important element of support which is not available from other grant programs.

Adoption of Revised Core Grant Guidelines

In order to control sharp increases in requested levels of support and, at the same time, preserve the intended purposes of the core grant, revisions of the 1976 Core Grant Guidelines were approved by the NCAB and the DRCCA Board of Scientific Counselors in the early part of 1981. The revised guidelines became effective October 1, 1981.

The Centralized Cancer Patient Data System (CCPDS) Grants

Objectives

CCPDS is a standard system for registering persons with reportable malignant neoplasms who are patients at Comprehensive Cancer Centers. Eligible patients were those first admitted to a center on or after July 1, 1977. All cases meeting certain requirements are reported to the Statistical Analysis and Quality Control Center (SAQC) in Seattle, Washington. SAQC is responsible for maintaining the system, analyzing the data, and acting as the coordinator for research activities.

Thirty-eight items of information are collected on each patient, including demographic characteristics, diagnosis, therapy, and survival. Standardized definitions of data items have been documented in the "CCPDS Data Acquisition Manual" (DAM). This manual also includes recommended procedures for abstracting, coding, submitting data to SAQC, and quality control.

Initially, standard definitions and codes were established for reportable patients and tumors, as well as for each of the 38 items. Criteria for quality control were set up to assess accuracy, completeness, and timeliness of reporting. There is a continuing effort to maintain inter-center comparability and compatibility with other national and international cancer reporting systems. CCPDS data are disseminated according to policies and procedures developed by a Policy Advisory Committee for that purpose.

Accomplishments

The CCPDS grants have resulted in a computerized patient data system in each of the centers. This system plus the quality control activities developed by SAQC have resulted in a higher quality, more efficient patient data system for the centers. In addition, these grants have supported statistical activities within the center to ensure better research uses of the system.

These grants were originally funded in 1977. To date, 20 cancer centers have been funded. Approximately 50,000 new cases are registered each year at SAQC.

Future Plans

At the May 7, 1982, meeting, the Board of Scientific Counselors, DRCCA, decided that funding of institutional CCPDS grants should be discontinued as of July 31, 1983. Institutional participation is expected with NCI support continuing for the SAQC headquarters.

Plans for future submissions of patient data to the SAQC center have not been developed. This program may be discontinued.

Cancer Centers Outreach Program

The Cancer Centers Outreach Program emphasizes planning, evaluation, pilot project development, and general cancer control program support. This requires a core of scientific and administrative staff that can develop detailed knowledge of the regional population patient loads, different and unusual demographic factors and disease characteristics in the region; develop broad program areas of emphasis; plan for the evaluation of control activities; and develop spin-off projects that can compete for separate funding on the basis of scientific merit and community support. In the past year, the outreach programs have stimulated development of a wide range of support for community hospitals, including multidisciplinary, multi-institutional consultative services for cancer diagnosis and treatment.

The Cancer Centers Outreach Program supports 24 comprehensive, clinical, or community cancer centers in the planning, development, and implementation of applied research in prevention and treatment programs. The Outreach Program will be succeeded by two new programs in FY 1983: the Cancer Control Research Units and the Cancer Center Science Program.

Cancer Control Research Units

The NCI's Division of Resources, Centers, and Community Activities has initiated two new directions for its cancer control effort with a combination of research programs intended to replace the Cancer Centers Outreach Program. The new programs are designed to meet the critical need for more cancer control research in both prevention (primary and secondary) and management (diagnosis, pretreatment evaluation, treatment, rehabilitation, and continuing care). A maximum of $7.5 million will be available for these programs in FY 1983.

In March, a request for applications (RFA) was issued for the first new program, entitled Cancer Control Research Units for Defined Population Studies (CCRUs). Successful applications will be awarded in FY 1983.

In defined populations, three types of activities may be supported using the CCRU grant mechanism:

1. Research to determine how, whether, and to what extent actions proposed for a particular cancer are effective for defined populations. These populations should be defined in such a way as to allow generalization to large segments of the U.S. population for purposes of cancer control program development.

2. Research to determine the optimal strategies for reducing incidence, mortality, or morbidity for a particular cancer(s) in a measurable way, and research on methods for efficiently implementing these strategies.

3. Selective implementation of strategies proven efficacious for particular cancer(s) and assessment of the efficacy and practicality of such strategies for large populations.

The CCRUs will be specialized research units and will require long-term support, involve multidisciplinary participation, and will need to have access to defined populations in order to measure the population impact of any cancer control activities. It is believed that a number of institutions or organizations in the United States have the "critical mass" of resources and qualified personnel to become research units of this type. This RFA is not intended to create a CCRU in a location where such a critical mass does not already exist.

A CCRU will be organized around a core group of highly competent investigators, each capable of obtaining peer-reviewed project support. Under a CCRU Director, investigators will receive project support for research using defined populations, for other approved studies, or for developmental research projects, or will seek other peer-reviewed funding support. A minimum of three defined population studies (a chemoprevention study may substitute for one of these studies) must successfully pass peer review and be approved before the CCRU application will be considered for funding. Highest priority for awards is being given to research involving: (1) cancers causing the greatest mortality/morbidity in the United States; (2) those cancers for which substantial risk has been associated with common exposures; and (3) those cancers for which apparently effective actions are available.

Cancer Control Science Program

The CCSP encourages development throughout the United States of core groups of researchers who will perform cancer control research studies (a minimum of three cancer control research projects that can successfully undergo review for scientific merit). Development funds for pilot projects of high scientific merit and with future promise of being supported as individual peer-reviewed research projects could be included. This program will be for a period of 5 years, and applications may be made at three different times in a year. Grant applications are due by August 15, 1982, for funding in FY 1983.

A second new program announcement, the Cancer Control Science Program (CCSP), was published in the March 1982 issue of the NIH Guide for Grants and Contracts.

Appendix I

Comprehensive Cancer Centers

1. Comprehensive Cancer Center, University of Alabama in Birmingham
   Birmingham, Alabama

2. Kenneth Norris, Jr., Cancer Research Institute
   University of Southern California
   Los Angeles, California

3. UCLA Jonsson Comprehensive Cancer Center
   UCLA School of Medicine
   Los Angeles, California

4. Yale University Comprehensive Cancer Center
   New Haven, Connecticut

5. Georgetown University/Howard University Comprehensive Cancer Center
   Vincent T. Lombardi Cancer Research Center
   Georgetown University Medical Center
   Washington, D.C.

   Howard University Cancer Research Center
   College of Medicine
   Washington, D.C.

6. Comprehensive Cancer Center for the State of Florida
   University of Miami School of Medicine
   Jackson Memorial Medical Center
   Miami, Florida

7. Illinois Cancer Council
   Chicago, Illinois

   Northwestern University Cancer Center
   Chicago, Illinois

   University of Chicago Cancer Research Center
   Chicago, Illinois

8. Johns Hopkins Oncology Center
   Baltimore, Maryland

9. Sidney Farber Cancer Institute
   Boston, Massachusetts

Comprehensive Cancer Centers (Cont.)

10. Comprehensive Cancer Center of Metropolitan Detroit
    Detroit, Michigan

11. Mayo Comprehensive Cancer Center
    Rochester, Minnesota

12. Columbia University Cancer Research Center
    College of Physicians and Surgeons
    New York, New York

13. Memorial Sloan-Kettering Cancer Center
    Sloan-Kettering Institute for Cancer
    Research/Memorial Sloan-Kettering Cancer Center
    New York, New York

14. Roswell Park Memorial Institute
    Buffalo, New York

15. Comprehensive Cancer Center
    Duke University Medical Center
    Durham, North Carolina

16. The Ohio State University Comprehensive Cancer Center
    Columbus, Ohio

17. Fox Chase/University of Pennsylvania
    Comprehensive Cancer Center

    The Fox Chase Cancer Center
    Philadelphia, Pennsylvania

    University of Pennsylvania Cancer Center
    Philadelphia, Pennsylvania

18. The University of Texas System Cancer Center
    M.D. Anderson Hospital and Tumor Institute
    Houston, Texas

19. Fred Hutchinson Cancer Research Center
    Seattle, Washington

20. The University of Wisconsin Clinical Cancer Center
    Madison, Wisconsin

Clinical Cancer Research Centers

1. University of Arizona Cancer Center
   Tucson, Arizona

2. City of Hope Research Institute
   Duarte, California

3. Northern California Cancer Program
   Palo Alto, California

4. University of California at San Diego
   La Jolla, California

5. Cancer Center of Hawaii
   University of Hawaii at Manoa
   Honolulu, Hawaii

6. University of Iowa Cancer Center
   Iowa City, Iowa

7. Ephraim McDowell Community Cancer Network, Inc.
   Lexington, Kentucky

8. Cancer Center, Tufts-New England Medical Center
   Boston, Massachusetts

9. Norris Cotton Cancer Center
   Dartmouth-Hitchcock Medical Center
   Hanover, New Hampshire

10. Cancer Research Center
    Albert Einstein College of Medicine
    Bronx, New York

11. Mount Sinai School of Medicine
    New York, New York

12. New York University Medical Center
    New York, New York

13. University of Rochester Cancer Center
    Rochester, New York

14. Cancer Research Center, University of North Carolina
    Chapel Hill, North Carolina

Clinical Cancer Research Centers (Cont.)

15. Oncology Research Center
    Bowman Gray School of Medicine
    Winston-Salem, North Carolina

16. University of Puerto Rico, Medical Sciences Campus
    San Juan, Puerto Rico

17. Roger Williams General Hospital
    Providence, Rhode Island

18. Memphis Regional Cancer Center
    Memphis, Tennessee

19. St. Jude Children's Research Hospital
    Memphis, Tennessee

20. The University of Texas Medical Branch Hospitals
    Galveston, Texas

21. MCV/VCU Cancer Center, Medical College of Virginia
    Richmond, Virginia

22. Vermont Regional Cancer Center, University of Vermont
    Burlington, Vermont

Laboratory Cancer Research Centers

1. Stanford University Medical Center
   Stanford, California

2. Scripps Clinic and Research Foundation
   La Jolla, California

3 La Jolla Cancer Research Foundation
   La Jolla, California

4. Armand Hammer Center for Cancer Biology
   The Salk Institute
   San Diego, California

5. Purdue University
   West Lafayette, Indiana

6. Worcester Foundation for Experimental Biology, Inc.
   Shrewsbury, Massachusetts

7. Massachusetts Institute of Technology
   Cambridge, Massachusetts

8. Center for Basic Cancer Research, Washington University
   School of Medicine
   St. Louis, Missouri

9. New York University Medical Center
   New York, New York

10. American Health Foundation
    New York, New York

11. Grace Cancer Drug Center
    Buffalo, New York

12. Case Western Reserve University
    Cleveland, Ohio

13. The Pennsylvania State University, College of Medicine
    Hershey, Pennsylvania

14. The Wistar Institute of Anatomy and Biology
    Philadelphia, Pennsylvania

15. Fels Research Institute
    Temple University Medical School
    Philadelphia, Pennsylvania

16. The University of Wisconsin, McArdle Laboratories
    Madison, Wisconsin

Cancer Centers Branch Publications Available

1. Guidelines for the Cancer Center Support Grant of the National Cancer Institute (January 1982).

2. RFA-NCI-DRCCA-CCB-82-6: "Cancer Control Research Units for Defined Population Studies," announced in NIH Guide for Grants and Contracts, Vol. II, No. 2., January 29, 1982, pages 15-18.

3. Cancer Control Science Program: Guidelines, April 1982, announced in the NIH Guide for Grants and Contracts, Vol. II, No. 2, March 26, 1982, p. 28-34.

4. Cancer Centers Administrative Profile Summary Report, April 1982.

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COMMUNITY OUTREACH AND REHABILITATION BRANCH

The Community Outreach and Rehabilitation Branch supports programs designed to:

A. Increase the transfer of cancer control activities from research centers to the community;

B. Develop effective cancer management capabilities within the community;

C. Use community research resources to increase knowledge in cancer control leading to a decrease in morbidity and mortality for patients;

D. Continue the development of rehabilitation devices and strategies;

E. Develop new approaches to the management of pain associated with cancer; and

F. Study the problem of optimal care for the terminally ill cancer patient.

Clinical Cooperative Group Programs

The reduction of cancer morbidity and mortality in the community setting is the goal of the Cooperative Group Outreach Programs. The objectives of these programs are to upgrade the skills of community physicians and other health professionals in the management of cancer patients and to increase the number of these patients receiving the best available care.

The mechanisms for achieving this goal are:

1. Strengthening and enlarging the affiliated hospital programs of the Cooperative Group to increase the number of community health professionals linked with the resources of the Cooperative Groups to participate in well-defined and monitored protocols for the management of cancer patients.
2. Providing support services to community physicians to maintain a high standard of patient care and data collection.
3. Instituting quality controls of patient management by the analyses of treatment data to assure high standards of care for patients entered on treatment protocols.
4. Providing continuing educational activities for community health professionals.

This program currently funds six Clinical Cooperative Groups (5 contracts and 1 grant) with a total annual budget of approximately 5 million dollars. These groups are:

1. Childrens Cancer Study Group (Contract No. NO1-CN-65374)
2. Eastern Cooperative Oncology Group (Contract No. NO1-CN-75348)

3. Northern California Oncology Group (Grant No. CA-24751)
4. National Surgical Adjuvant Breast Project (Contract No. NO1-CN-85335)
5. Radiation Therapy Oncology Group (Contract No. NO1-CN-75335)
6. Southwest Oncology Group (Contract No. NO1-CN-65285)

This program has accomplished the technology transfer of optimal patient management techniques from the research community to the community-at-large. To date, more than 2000 community physicians in more than 700 hospitals have participated in this program and more than 4000 community patients have been enrolled into Group Protocol studies. As a "demonstration project," this program was originally intended to be completed in three years and was subsequently extended for an additional two years ending in 1982.

Projects Publication

Begg, Colin B., Ph.D., Paul P. Carbone, M.D., Paul J. Elson, M.S., and Marvin Zelen, Ph.D., Participation of community hospitals in clinical trials: Analysis of five years of experience in the Eastern Cooperative Oncology Group. The New England Journal of Medicine. pp. 1076-1080, May 6, 1982.

Community Hospital Oncology Programs (CHOPS)

This program field tested, in multiple settings, a model approach to the development of community hospital cancer programs. The CHOP Model was derived from the experiences of seven pilot Clinical Oncology Programs supported through FY 1980. The purpose of these community hospital oncology programs is to provide evidence that implementation of the CHOP model in a community will improve the scope and quality of care for cancer patients over that received prior to development of the program.

In the development and implementation of each program, the cooperating hospitals and health care professionals will:

1. Define criteria for cancer patient care through the development of management guidelines;

2. Implement a program to encourage community cancer care practices in accordance with these criteria for care;

3. Use a data management system (e.g., through upgraded tumor registries) to assess the extent to which community cancer care practices correspond to the recommended criteria; and

4. Use the information obtained to correct, modify, and improve the clinical oncology program and document effective changes in community cancer care.

Twenty-three CHOP contractors are completing 18 month planning contracts. Participating communities range from large metropolitan settings to more remote urban and rural settings and involve single institutions and multi-institutional programs involving as many as 10 hospitals.

COMMUNITY HOSPITAL ONCOLOGY PROGRAM

Contract Number	Institution	Principal Investigator
SINGLE HOSPITAL		
CN-00526	Georgia Baptist Medical Center Atlanta, Georgia	Mario Ravry, M.D.
CN-05527	Deaconess Hospital Evansville, Indiana	Thomas G. Lutz, M.D.
CN-05529	Our Lady of Lourdes Memorial Hosp. Binghamton, New York	Robert E. Enck, M.D.
CN-05530	Marshfield Medical Foundation Marshfield, Wisconsin	Robert H. Greenlaw, M.D.
CN-15547	California Medical Center Los Angeles, California	Joseph F. McKernan, M.D.
CN-15549	Hackensack Hospital Hackensack, New Jersey	Charles Vialotti, M.D.
CN-15550	Memorial Medical Center Savannah, Georgia	Ronald F. Goldberg, M.D.
CN-15551	Mercy Hospital Scranton, Pennsylvania	William S. Heim, M.D.
CN-15553	Riverside Methodist Hospital Columbus, Ohio	Joseph A. Bonta, M.D.
CN-15557	St. Luke's Hospital of Bethlehem Bethlehem, Pennsylvania	Richard J. Torpie, M.D.
CN-15558	St. Paul Hospital Dallas, Texas	Ronald F. Garvey, M.D.
CN-15560	St. Vincent Medical Center Los Angeles, California	S. Barry Sakulsky, M.D.
CN-15561	South Fulton Hospital Tri-City East Point, Georgia	John Warner Ray, M.D.
SMALL COMMUNITY		
CN-05525	Southwest Washington Hospital Vancouver, Washington	Robert W. Olwine, M.D. Eugene B. Blizzard, M.D.
MULTI HOSPITAL	(*Number of institutions participating)	
CN-05528	Penrose Hospital (4*) Colorado Springs, Colorado	Paul N Anderson, M.D.
CN-15546	Borgess Medical Center (2*) Kalamazoo, Michigan	Leo Zelkowitz, M.D.
CN-15548	Christ Hospital (10*) Cincinnati, Ohio	Richard Meyer, M.D.
CN-15552	Methodist Hospital (3*) Brooklyn, New York	Sameer Rafla, M.D.
CN-15554	Roanoke Memorial Hospital (4*) Roanoke, Virginia	Charles L. Crockett, M.D.
CN-15555	St. Francis Hospital of Wichita (4*) Wichita, Kansas	Harry E. Hynes, M.D.
CN-15556	St. Louis Park Med. Res. Found. (7*) Minneapolis, Minnesota	J. Michael Ryan, M.D.
CN-15559	St. Peter's Hospital (4*) Albany, New York	Robert W. Sponzo, M.D.
CN-15562	Toledo Hospital (9*) Toledo, Ohio	Charles D. Cobau, M.D.

Pain Programs

DRCCA supports projects in pain research ranging from the neurophysiology of pain to structured complex approaches to the study and management of pain of cancer patients. Pain is one of the most feared consequences of cancer. Severe pain generally occurs in advancing and terminal disease, and pain may also be an early manifestation of cancer or its presenting symptom. Cancer pain has been the focus of considerable attention and concern for clinicians, patients, their friends and families, the general public, and the Government. However, it is now the consensus that no adequate data base exists from which to determine the true magnitude of the cancer pain problem. DRCCA has initiated pilot studies of cancer pain with the goal of gathering valid data defining the incidence and natural history of pain in cancer. Under the contract program Pain Control in Cancer, seven institutions (Contract Nos. NO1-CN-95417, 95486, 95487, 95488, 95489, 95490, 95491) are participating in a collaborative study to demonstrate that pain control for cancer patients is best instituted early in its onset after careful planning and evaluation by a multidisciplinary team of experts. This program addresses the management of pain associated with advanced and metastatic disease and chronic pain associated with localized disease.

Projects Publications:

Kremer, E., Atkinson, J.H., and Ignelzi, R.J.: Measurement of pain: Patient preference does not confound pain measurement. Pain. (in press).

Kremer, E., Atkinson, J.H., and Ignelzi, R.J.: Pain measurement: Construct validity of the affective dimension of the McGill Pain Questionaire with clinic benign pain patients. Pain. (in press).

Kremer, E., Atkinson, J.H., and Ignelzi, R.J.: Pain measurement: The affective dimensional measure of the McGill Pain Questionnaire with a cancer pain population. Pain. (in press).

Atkinson, J.H., Kremer, E., and Ignelzi, R.J.: The diffusion of pain language with affective disturbance confounds differential diagnosis. Pain. (in press).

Daut, R.L. and Cleeland, C.S.: The prevalence and severity of pain in cancer. Cancer. (in press).

Pattern of Care Study in Radiation Therapy

This landmark study of the American College of Radiology is in its seventh year. This represents the first effort by a major cancer care specialty to systematically assess national patterns of care and develop educational strategies to improve quality of cancer care practices. Initial and follow up process surveys on ten cancer sites and outcome surveys on five sites have been completed. National benchmark outcomes with four year actuarial results have been completed for carcinoma of the cervix, Hodgkin's Disease and head and neck sites. Follow up process outcome surveys are planned. It is anticipated that this study will result in a permanent quality assurance program for radiation therapy when federal support is complete.

Projects Publications:

Kramer, S.: An overview of process and outcome data in the patterns of care study. Int. J. Radiat. Oncol. Biol. Phys. 7:795-800, 1981.

MacLean, C.J.: Variation in workup and treatment procedures among types of radiation therapy facilities: The patterns of care process survey for three head and neck sites. Cancer. 48:1346-52, 1981.

Hanks, G.E., Herring, D.F., and Kramer, S.: Patterns of care outcome studies: Results of the national practice in seminoma of the testis. Int. J. Radiat. Oncol. Biol. Phys. 7:1413-1417, 1981.

MacLean, C.J.: Discriminant analysis of radiation therapy procedures: The patterns of care process survey for carcinoma of the larynx. Cancer. 49:229-233, 1982.

Hanks, G.E., Kinzie, J.J., and Herring, D.F., Kramer, S.: Patterns of care outcome studies in Hodgkin's Disease: Results of the national practice and implications for management. Can. Treat. Rep. April, 1982.

Kramer, S., Hanks, G.E., Herring, D.F., and Davis, L.W.: Summary results from the facilities master list: Surveys conducted by the patterns of care study. Int. J. Radiat. Oncol. Biol Phys. April, 1982.

Hanks, G.E., Kramer, S., Diamond, J.J., and Herring, D.F.: Patterns of care outcome survey: National outcome data for six disease sites. Am. J. Clin. Oncol./Cancer Clin. Trials. May, 1982.

Hanks, G.E., Kinzie, J.J., White, R.L., and Herring, D.F., Kramer, S.: Patterns of care outcome studies: Results of the national practice in Hodgkin's Disease. Cancer. (in press).

Hanks, G.E., Herring, D.F., and Kramer, S.: Patterns of care outcome studies: Results of the national practice in cervix cancer. Cancer. (in press).

Community Clinical Oncology Program

A large scale cancer control effort, the Community Clinical Oncology Program (CCOP) which involves practicing community oncologists in the NCI clinical trials programs, will be initiated in Fiscal Year 1983. The purpose of the program is to utilize as a resource the increasing number of highly trained oncologic specialists who have entered community practice in recent years. Combining the expertise of community physicians with ongoing clinical research projects will result in a dynamic development and exchange of the newest clinical treatment research findings at the community level.

The CCOP initiative is intended to meet the needs of cancer patients by utilizing the trained specialists now practicing in community hospitals and clinics and establish a system of community clinical oncology programs which will participate in clinical research trials. Over 80 percent of patients with cancer are treated in the community with only a small number entering clinical trials. The Division of Cancer Treatment (DCT) of NCI supports a national

clinical trials program largely through academic centers. These have included (1) multimodal national and regional cooperative groups, (2) groups in which the investigators have a particular expertise (such as pediatricians), (3) groups that are designed to deal primarily with high technology single modality studies and (4) groups that are specifically disease-oriented. Additional large cancer centers are involved in implementation of local clinical research protocols.

Over the past decade, increasing numbers of highly trained clinical cancer specialists, experienced in clinical research and protocol care, have been entering private practice in the community. Experience within several Cooperative Groups has indicated that physicians caring for cancer patients in the community can maintain high quality clinical research activities similar to that of the academic centers. Evidence exists that new technology can be transferred effectively by having community physicians participate in clinical research activities.

CCOP And Research Base Affiliation

Each Community Clinical Oncology Program must have an affiliation with a nationally recognized clinical cancer research base. These may be clinical or comprehensive cancer centers, national or regional cooperative groups. Participating community programs will be required to enter or refer into NCI-approved clinical trials, designated as high priority by a research base with which the CCOP is affiliated. These research bases may be national or regional multi-disease cooperative groups, specialized cooperative groups or cancer centers currently participating in NCI approved clinical research protocols. Participants are encouraged to enter patients with early stage disease with common cancers and to enter or refer, if appropriate, patients with uncommon cancers.

Objectives of the Community Clinical Oncology Program

The CCOP initiative is designed:

A. To bring the advantages of clinical research to cancer patients in their own communities, by having practicing doctors and their patients participate in clinical treatment research protocols, and thus foster an exchange between clinical research and cancer control.

B. To reduce national mortality by speeding the transfer of newly developed cancer treatment technology to widespread community application.

C. To provide a basis for involving a wider segment of the community in cancer control activities and investigate the diffusion of cancer therapy advances in community medical practices. The diffusion hypothesis presumes that introduction of quality-controlled clinical research trials in the community will also benefit those patients not treated as part of this protocol.

D. To develop programs to serve as part of a broadly based nationwide resource for quality-controlled distribution of increasing numbers of experimental anti-cancer agents.

E. To facilitate community participation in future cancer control and prevention research activities planned by NCI.

Funding Mechanism and Amount of Support

Awards will be in the form of Cooperative Agreements, a preferred mechanism for funding NCI Clinical Trials Programs. The Cooperative Agreement is an assistance relationship which features substantial government involvement in the scientific conduct of a program. The clinical research activities planned by the CCOPs in conjunction with their affiliated research bases are similar to those conducted by the clinical cooperative group members supported by the Division of Cancer Treatment. Use of the cooperative agreement mechanism will assure consistency and quality control procedures in the application of clinical trials in the community setting. Cooperative agreements are essentially a partnership between the government and the recipients of the awards.

It is anticipated that up to ten million dollars will be allocated for the CCOP in FY 1983. Initially, CCOP will be a three-year program.

Unique Features of CCOP

The CCOP is a major long-term effort to stimulate cancer control activities through direct community support. This attempt should encourage cooperation among community physicians and clinical research resources (cancer centers and cooperative clinical trials groups). These initial community cancer control efforts are readily evaluated and should be followed by other systematic cancer control efforts in areas such as prevention and early detection.

Rehabilitation Program

This program seeks to reduce the morbidity from cancer and its treatment through stimulating study, demonstration, and research in new techniques of rehabilitation that have specific applicability to the physical, cosmetic, and functional problems associated with cancer.

The comprehensive nature of cancer rehabilitation determines support for a variety of projects which seek to achieve the cancer patients' early adjustment and re-entry into the everyday world of work, social activity, and physical functioning.

Contracts

Four contracts support a Training Program for Maxillofacial Prosthodontists and Maxillofacial Dental Technicians, (Contract Nos. NO1-CN-05458, 05522, 05523, 05524).

The projects funded by contract went beyond the training routinely available in the existing curricula of dental schools. Eligible applicants for this program were graduate dentists wishing to specialize in oro-facial restoration using non-living

materials. Didactic lectures, clinical experiences, and laboratory procedures are set out in the RFP workscope.

To ensure adequacy of performance, each contractor developed and submitted to the project officer: 1) an evaluation plan, 2) a training curriculum, 3) a patient access report, and 4) a semiannual training or progress report.

These documents will provide the basis for a model maxillofacial training program for dental schools wishing to initiate such a program independent of federal funding. The Evaluation Plan of the four contractors was reviewed by NCI and four expert consultants. Two contractors requested six month's extensions which were granted.

Grants

The Rehabilitation Program supports 21 grants which presently investigate six major areas of cancer rehabilitation.

1. Grants that develop, field test or demonstrate new skills, coping strategies, social support systems to improve the effectiveness of rehabilitation approaches. Seven grants fall in this category (Grant Nos. CA-20615, 26868, 26878, 27630, 27683, 27766, 27807).

2. Prostheses Development, Restoration, and Reconstruction - Cancer treatment frequently compromises anatomical structures and physiological functions. New devices and new procedures utilizing both living tissue and non-living materials are studied for specific application to cancer restorations. These projects pursue their investigation at both the laboratory and clinical stage. Five grants fall into this category (Grant Nos. CA-17945, 19761, 23571, 25650, 29046).

3. Host Maintenance - The patient's own physical strength and recuperative resources are an essential requisite for cancer rehabilitation. Clinicians and researchers increasingly recognize the potential of nutrition as a rehabilitation modality directly related to the success or failure of the rehabilitative endeavor. There are currently three active grants in this category (Grant Nos. CA-17928, 28005, 28072).

4. Patients' Reaction to Illness - Cancer patients exhibit a range and complexity of reactions to their illness in both the physical and psychological sphere. Such reactions need structured explorations for better understanding and planning. Exaggerated and untoward reactions mitigate against early, effective rehabilitation. Currently two grants study reaction to illness (Grant Nos. CA-19344, 24079).

5. Programmatic approaches involving demonstration of an institutional or department level plan for managing a major rehabilitation program in home care for terminal cancer, in which the objective is rehabilitation not nursing care or treatment. Such projects involve a variety of disciplines, resources, and services centrally coordinated and supervised. Two grants fall into this category (Grant Nos. CA-26779, 20396).

6. Measurement and Evaluation - While each funded project includes an evaluation component, there is a need to develop universal indexes of

measurements that can be applied independently to a given rehabilitation program or a single rehabilitation intervention. These projects address this need (Grant Nos. CA-27912, 25289).

The majority of these grants are in the final year, six having already submitted their final report. To ensure that every treated cancer patient has access to adequate, effective rehabilitation remains a primary NCI objective. There is an increased need for improved rehabilitation capabilities in the area of physical and physiological maintenance throughout the course of vigorous treatment as well as immediate initiation of restoration following treatment. Investigator initiated grant applications are encouraged over the next year.

Oncology Nursing Education Program

In 1979, San Jose State University (No. 95480) and the University of Alabama (No. 95428) were awarded contracts to develop and implement a model postmaster's one-year fellowship program in oncology nursing. The project faculty of the two schools of nursing have collaborated in designing a model curriculum and evaluating its effectiveness. The major objective of the program is to help resolve the nationwide shortage of qualified oncology nurse clinicians by providing advanced academic preparation to nurse educators who will then develop and upgrade oncology programs at the graduate, undergraduate and continuing education levels.

Participants were selected from all regions of the country. A second group of fellows is currently enrolled. A 15 month follow-up evaluation plan was implemented with the first group of fellows in April, 1982. In September 1982, a third group will be admitted to the University of Alabama program.

In 1979, a grant was awarded to the Fred Hutchinson Cancer Research Center to develop a Community-Based Cancer Nursing Education Program for Registered Nurses throughout the Pacific Northwest and Alaska. To date, over 324 nurses have completed the 80 hour curriculum in 13 communities. A pre and post program evaluation has been accomplished and the lecture series of the 80 hour curriculum along with the program's audio-visuals is in an exportable format for distribution.

Hospice Program

Three projects in Implementation of the Hospice Concept for the Care of Terminal Cancer Patients with a home care program and a backup in-house facility (Contract Nos. NO1-CN-85392, 85375, 75391) have been completed. These projects provided a demonstration of comprehensive terminal care given in three different settings, i.e., a nursing home, a community hospital, and a health maintenance organization.

A collaborative, descriptive study developed by the hospice contractors and NCI program staff was completed. The study focused on a thorough description of care in the three settings which included a longitudinal assessment of the patient and the bereaved family members (significant others). In describing the hospice patient population, age, sex, socio-economic status, medical condition, and other pertinent characteristics were recorded. The initial report with preliminary analyses will be available in the fall.

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NATIONAL ORGAN SITE PROGRAMS BRANCH

The National Organ Site Programs Branch currently consists of grant supported National Projects of targeted cancer research. Each Project is a planned research effort oriented towards cancer at a specific organ site. Currently there are National Organ Site Projects concerned with cancers of the urinary bladder, large bowel, pancreas, and prostate. The planning, direction, and coordination of each Project are provided at headquarters outside the NCI. The four National Project Directors are assisted in planning and administration by the headquarters staff and by a chartered committee of active research scientists recruited from institutions throughout the nation. Grant applications are received by the headquarters and are reviewed by the four individual committees with final review by the National Cancer Advisory Board. Applications which are judged scientifically meritorious and relevant to the aims of the Project are recommended to the NCI for funding.

Each National Project Director is a recognized clinical or laboratory scientist with a strong interest in, and professional identification with, a specific organ site cancer. The National Bladder Cancer Project is under the direction of Dr. Gilbert H. Friedell, St. Vincent Hospital, Worcester, Massachusetts; the National Large Bowel Cancer Project, Dr. Edward M. Copeland, M.D. Anderson Hospital and Tumor Institute, Houston Texas; the National Pancreatic Cancer Project, Dr.Isidore Cohn, Jr., Louisiana State University School of Medicine, New Orleans, Louisiana; and the National Prostatic Cancer Project, Dr. Gerald P. Murphy, Roswell Park Memorial Institute, Buffalo, New York.

In May 1982, the National Cancer Advisory Board recommended that the Organ Site Programs be reorganized as a National Organ Systems Program with a mission to focus on the four sites currently recognized, but to continuously appraise progress at other sites in order to identify those which might require specialized attention. In addition, the Breast Cancer Program will be integrated into the Organ Systems Program Branch. A single Coordinating Center external to the NCI would have two divisions at the outset: Genitourinary and Gastrointestinal. The Coordinating Center would be responsible for the organization, planning, coordination, and overview of the basic and clinical research components of the program. Communication between the clinical and laboratory segments would be maintained through workshops, and conferences, and fostered through other novel mechanisms yet to be developed. Peer review for the research grant applications would be performed by Study Sections within the Division of Research Grants.

NATIONAL BLADDER CANCER PROJECT

The primary goal of the National Bladder Cancer Project (NBCP) is to sponsor and encourage laboratory and clinical research directed toward improving the techniques available for detecting and diagnosing, preventing and/or controlling cancer of the urinary bladder.

The Project is based entirely on investigator-initiated grants. Qualified investigators are encouraged to submit grant applications to accomplish specific objectives. All grant applications submitted to the NBCP are evaluated by the Bladder Cancer Subcommittee (BCS) of the Bladder and Prostatic Cancer Review Committee for relevance to the needs of the project and for overall significance toward the achievement of the NBCP goals.

A collaborative effort is supported by the NBCP for prospective studies of patients with bladder carcinoma. The organization of the National Bladder Cancer Collaborative Group A (NBCCGA) is based upon the concept that bladder cancer is a progressive disease and that an increased understanding of the progression under treatment for various subgroups of patients will contribute to improved therapy through improved diagnosis and classification of patients. Consequently, a basic protocol of the NBCCGA is the surveillance of all patients with bladder cancer admitted by participating physicians. When the most suitable treatment selection is not known, randomized clinical trials are established to provide the data from which such a decision can be derived.

The broad goals of the NBCCGA are: to assess and characterize patients, their neoplasms, and the fields from which the neoplasms arise; to evaluate new diagnostic and marker techniques for better classification of the patients and their neoplasms; to verify application of existing treatment modalities; to clarify the role of radiation in combined therapy; and to evaluate a variety of agents singly and in combination, intravesically and systemically, alone and as adjuvant to surgery and/or radiation therapy.

Accomplishments

The results of investigator-initiated efforts in the NBCP have been outstanding. By expanding the close working relationship between the Headquarters and the BCS to include the larger scientific community, a total of 246 investigators (85 principal investigators) representing 24 different disciplines were recruited from 52 different institutions into the program. Nine additional institutions have been represented through membership on the BCS. A total of 354 grant applications have been reviewed to date, out of which 96 different projects have been funded. Twenty of these projects were intradepartmental, 54 were interdepartmental and 48 were interinstitutional.

With the encouragement and coordination provided by NBCP Headquarters and the BCS, laboratory investigators have provided essential basic information and have developed very useful experimental models of bladder cancer while a network of sensitized communicating and cooperating clinical research workers have made striking changes in the approach to the management of this disease by the practicing urologist.

Epidemiology

The accumulation of definitive new information on the epidemiology of bladder cancer has slowed considerably. This is due in part to the apparent confounding influence

of cigarette smoking as a major contributing factor in etiology of the disease. One recent study examined the hypothesis that defects in tryptophan metabolism might contribute to a higher incidence of bladder cancer based on the observed action of tryptophan as a tumor promotor in experimental animals (Friedlander and Morrison, 1981). This study showed that tryptophan excretion was not significantly different between bladder cancer patients and controls when adjusted for age, sex, and smoking status.

Carcinogenesis

Numerous bladder carcinogenesis studies are ongoing in the NBCP utilizing the following carcinogens and/or their metabolites: N-butyl-N-(4-hydroxybutyl)nitrosamine (BHBN) (Murphy and Irving, 1981), benzidine (Morton et al, 1981), phenacetin (Vaught et al, 1981), and N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) (Cohen et al, 1982; Mattammal et al, 1981; Swaminathan et al, 1981). These studies range from the identification of morphologic features in both preneoplastic and frank neoplastic lesions to metabolism and molecular interactions with cellular nucleic acids and proteins.

The activation of carcinogens -- or procarcinogens -- by various tissues and various pathways is gradually leading to a better understanding of molecular events in the carcinogenesis process for particular compounds. One of the more exciting findings has been the observation that prostaglandin endoperoxide synthetase (PES) from kidney or bladder tissue specifically transforms (oxidizes) a variety of compounds to carcinogenically active species (Cohen et al, 1981; Davis et al, 1981; Zenser et al, 1981; Zenser et al, 1982). The separable characteristics of the cyclooxygenase and hydroperoxidase activities of PES, combined with substrate and inhibitor studies, implicated the prostaglandin hydroperoxidase activity as the activating catalyst.

Other studies using FANFT (Swaminathan et al, 1981) and liver microsomal metabolites of phenacetin (Vaught et al, 1981) have demonstrated that these bladder carcinogens can covalently bind to nucleic acids and cause mutagenicity in a restricted subline of Salmonella typhymurium. Further investigations of the nucleic acid adducts formed and of the actions of antagonists and nucleic acid repair processes are currently underway.

Recent progress has been made by several laboratories toward establishing normal transitional epithelial cells in culture as model systems for bladder carcinogenesis. Those efforts employing a growth substratum derived from connective tissue have been most successful. An in vitro system for cell growth using salt-extracted bovine articular cartilage has also been employed to discriminate normal non-invasive cells from invasive and highly metastatic cells according to the depth and rate of cellular invasion of the substratum (Pauli et al, 1981). It was further found that the natural resistance of unextracted cartilage to tumor invasion is due at least in part to the presence of tissue derived proteinase inhibitors (Pauli et al, 1981).

Further studies of multi-stage carcinogenesis have shown that the simple ulceration of urinary bladders of Fischer 344 rats (by freezing) was found sufficient to effect tumor initiation in 30 percent of animals fed a routine laboratory diet. That is, FANFT or other known exogenous initiators were not necessary to induce bladder tumors in these animals (Cohen et al, 1982). These observations extend the importance of cell division in the process of tumor initiation.

Diagnosis/Classification

Recent advances in cytogenetic techniques have shown that up to 70 percent of solid bladder tumors may now be accessed for the detection of abnormalities. Using these methods it was shown that 32 of 50 papillary tumors had marker chromosomes and 11 of 12 of these tumors which recurred had at least one marker (Sandberg, 1981). Thus, the presence of markers in these tumors may be indicative of the likelihood of recurrence and/or of progression of such tumors.

Improvements in flow cytometric (FCM) evaluation of bladder irrigation specimens have made this technique a viable adjunct to cystoscopy and cytology for patient evaluation. FCM agreed with cystoscopy and cytometry in 80 percent of the cases investigated with regard to tumor stage and grade (Devonec et al, 1982). Further, evaluation of patients receiving intravesical BCG therapy for superficial bladder cancer indicated that FCM could predict tumor recurrence by as much as 12 months before it is evident cystoscopically (Klein et al, 1981).

Immunology

A variety of immunologic approaches have been used to understand, evaluate, and treat bladder cancer patients. Two separate studies showed that tumor antigen-induced suppressor cells are responsible to a large extent for the impaired immune response seen in bladder cancer patients as judged by decreased lymphocyte proliferation and cytotoxicity (Bean, 1981; Spina et al, 1981).

After considerable effort, there is now promise that bladder tumor-enriched antibodies can be produced by hybridoma cells prepared from animals challenged with either established in vitro cell lines or with cells isolated from fresh tumors (Boxer et al, 1981; Hellstrom et al, 1982). One of these antibodies, identified as 2H5, gave significant binding to membranes from five of seven transitional cell carcinomas but not to membranes from any other tissues. The antigen bound to a 140,000 dalton protein which is detectable in bladder transitional cell carcinomas but to a much lesser extent in normal bladder tissue.

Studies of interferon showed that both T- and null cell lymphocytes can be stimulated by Staphylococcus aureus protein A to produce γ-interferon, although phytohemagglutinin is the best stimulus for this purpose (Catalona et al, 1981; McCool et al, 1981). Interestingly, cells from bladder cancer patients showed a greater response to protein A than did cells from controls or from patients with other urologic tumors.

Related studies developed a T-cell hybridoma which produces macrophage activation factor (MAF), a substance capable of activating macrophages to be tumoricidal (Ratliff et al, 1982). This factor requires a lipopolysaccharide for its action and is distinct from γ-interferon.

Chemotherapy

A variety of methods have been utilized to evaluate chemotherapy approaches and devise individualized therapy regimens. Thus, tumor tissues are either dispersed and introduced into monolayer or soft agar culture systems or minced and innoculated into athymic (nude) mice for examinations of the tumoricidal effects of various cytotoxic agents. Each of these systems has recently demonstrated the potential of predicting the best chemotherapy for the individual tumor or tumor patients (Day et al, 1981; Stanisic et al, 1981).

A recent study was carried out comparing radiation vs cis-platinum actions against

human bladder transitional cell carcinomas grown in nude mice (Kyriazis et al, 1982). This study demonstrated a synergistic effect of the two treatment regimens with optimal results obtained when cis-platinum was given at 6 days post-radiation. These results offer encouraging guidelines for chemotherapy regimens in humans.

Clinical Studies

In a longitudinal study conducted in several collaborating institutions, an analysis was made of recurrence of disease in patients with transitional cell carcinoma. The probability of early recurrence was found to be associated with the number and size of visible tumors, the histologic grade and depth of invasion, and the presence of dysplasia and hyperplasia in the non-tumor bearing areas of the bladder. Progression of disease with respect to depth of invasion and extension beyond the bladder was found to be related to depth of invasion at initial diagnosis, histologic grade, tumor size, and the presence of moderate to severe dysplasia (Cutler et al, 1982).

Urinary cytology has taken an important place in the evaluation of patients with transitional cell carcinoma. Cytology can provide highly useful prognostic information as a supplement to cystoscopy and bladder biopsy in the clinical evaluation of each patient. Positive cytology appears to be a predictive factor in patients at high risk for recurrence of the primary bladder tumor (Friedell et al, 1982).

A prospective study of patient tolerance and pathologic downstaging was conducted in a collaborative effort using 4,000 RAD preoperative irradiation followed by prompt cystectomy and urinary diversion in patients with muscle-invading bladder cancer. The results supported the rationale of using full dose adjuvant preoperative radiation therapy to downstage and sterilize unresected pelvic micrometastases and yet maintain a short interval between diagnosis and cystectomy (Shipley et al, 1982).

A recent study of 52 patients has indicated that intravesical instillation of bacille Calmette-Guerin (BCG) as a site-directed immune stimulant (33 patients) is more effective in preventing superficial bladder tumor recurrence than is thio-TEPA (19 patients) over a prolonged period of therapy (Brosman, 1981).

Emphasis and Projections

Epidemiology

Considering the international opportunities and interdisciplinary approaches now available, more attention should be given to epidemiology. Epidemiologists need to work more closely with clinicians to discern epidemiologic correlates with the natural history of the disease(s) -- to determine factors associated with recurrence, with high grade and with low grade lesions. From such studies may come a new understanding of how the processes involved can be prevented, delayed, or reversed.

Carcinogenesis

A greater sensitivity to biologic events in studies of initiation, promotion, and invasion is needed in addition to the current emphasis on chemical events. Such events should include differentiation/dedifferentiation, tumor angiogenesis and stromal epithelial cell relationships and interactions. New studies should include lower dosage levels of carcinogens and co-carcinogens which are more in line with human exposure and should make further efforts to detect and evaluate the earlier, pre-malignant state of the disease. The period of support for selected animal studies should be increased from three to four or five years so that long term studies, particularly those with lower dosages of carcinogen and co-carcinogens can be conducted. Macromolecule interactions with carcinogens should be studied more

intensively at a mechanistic level. The qualitative, quantitative, and kinetic relationships between carcinogen-macromolecule interaction and tumor induction should be examined.

Diagnosis

Sufficient technology (i.e., flow cytometry) and cytologic markers (i.e., ABH antigens, hyperploidy, and marker chromosomes) for malignant cells are now available to justify clinical trials using the cellular content of urine samples as the basis for classification and prognostic evaluation. Having established markers for overt bladder cancer lesions, there is now a need to develop systems most effective for the diagnosis of early lesions, particularly for diagnosing pre-high grade lesions. With the aid of the newly developing computer model, optimal screening strategies for populations at given probabilities of risk should be defined.

Treatment

Studies on the pathogenesis and etiology of the silent lesions which are diagnosed late after muscle invasion and metastases should be specifically emphasized. It is important to define further the need for and efficacy of individualization of therapy by matching a specific drug regimen to the individual tumor. New drugs should be sought which have a high propensity to concentrate in urine. The search for potentially effective drugs beyond the current arsenal being tested with other cancers should continue. Intravesical and systemic approaches should be compared using a variety of agents singly and in combination. Treatment regimens should be developed in concert with efforts to detect *in situ* lesions earlier in order to provide alternatives to cystectomy for this phenotype when found widespread in the bladder epithelium. The effect of reducing exposures to all known bladder carcinogens or promoters in patients who have already had an initial bladder tumor should be evaluated.

Other Program Activities

Since 1974, the NBCP has sponsored annual Investigators' Workshops for the purpose of facilitating communication and interaction among the laboratory and clinical elements in the Project. This effort has been one important means through which a coordinated project effort is achieved. It not only encourages the exchange of ideas and materials, but several collaborative efforts have developed from the workshop discussions.

The next workshop, scheduled as the Second National Bladder Cancer Conference to be held in January 1983, is currently being developed. This conference will be co-sponsored by the American Urological Association and will "double" as one of the AUA regional meetings. Major addresses will be given on triggering the cellular change to neoplasia, altered gene products, mechanism of invasion, metastatic process, flow cytometry, ploidy and nuclear changes. General discussion sessions and mini-workshops as well as poster sessions will be used to present the latest and most important research findings which provide a scientific basis for advances in the clinical management of bladder cancer. The meeting will be open to anyone interested in attending.

Members of the Headquarters Staff have continued collaboration with Dr. Leon Ellwein of Science Applications, Inc., in the development of a computerized simulation model of bladder cancer (clinical disease) which can be used as a tool for planning and for testing hypotheses of various diagnostic and therapeutic intervention strategies.

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NATIONAL LARGE BOWEL CANCER PROJECT

The National Large Bowel Cancer Project, with headquarters at The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, sponsors multidisciplinary basic and clinical programs of investigator-initiated research designed to examine the biology and promote the control of colon and rectal cancer.

Accomplishments

Biology, Cause, and Prevention of Large Bowel Cancer

The identity and isolation of mutagens formed during the cooking of meat has progressed (Weisburger et al. 1981). Efforts are now being directed at blocking mutagen formation. Soy protein (15%) reduces the amount of extractable mutagenic activity by more than 90%. Chlorogenic acid and butylated hydroxyanisole (BHA) are also highly inhibitory. Wilkins et al. (1980) are continuing their efforts to characterize mutagenic bacterial products from human feces.

Inhibition of methylazoxymethanol (MAM) acetate-induced colonic neoplasms in mice has been demonstrated using several phenols that are widely consumed in the diet as food additives or are naturally occurring constituents of fruits and vegetables (Wattenberg 1981a, 1981b). These phenolic compounds had varied effects on the NAD^+ -dependent alcohol dehydrogenase activity in the mouse liver and large bowel *in vitro*.

Onishi et al. (1982) are investigating the biotransformation of quercetin, a naturally occurring product with carcinogenic activity, by rat tissues (liver, kidney and intestinal mucosa). One non-mutagenic kidney metabolite was tentatively identified as isorhamnetin; a second unidentified metabolite of quercetin was mutagenic, and the structural features which appear to be essential for mutagenic activity have been identified. The formation of azoxymethane and other azoxy compounds during the biological oxidation of amines has also been studied (Fiala et al. 1981).

The inhibition of chemically induced colon carcinogenesis at various stages of neoplastic transformation by a variety of compounds is under intense study. Particular attention is being directed at fiber, vitamins, and at various minerals (Jacobs et al. 1981). Using an epidemiologic approach, Enstrom (1981, 1982) is assessing the role of diet in colorectal cancer etiology. Experiments conducted by Goldin and Gorbach (1981) suggest that a variety of factors, including antibiotics and diet, affect the metabolism and excretion of three different classes of procarcinogens and that a concommitant reduction in fecal bacterial enzyme activity explains these metabolic and excretory changes. The acute and chronic effects of dietary cholic acid on colonic epithelial cell proliferation have been described (Deschner et al. 1981), as has the effects of various bile acids on the absorption of carcinogens in the colon of rats and guinea pigs (Rose and Nahrwold 1982).

It has been determined that the colon is an active site of prostaglandin (PG) synthesis (Craven and DeRubertis 1981a), products which induce changes in cAMP and cGMP metabolism in this tissue. These latter factors have been implicated in the control of colonic epithelial cell proliferation (Craven and DeRubertis (1981b). Further studies in rat colon support the existence of an arachidonic acid responsive pathway for carcinogen activation which is in part coupled to cyclooxygenase and PG synthesis. This may represent an important alternative route of local colonic xenobiotic metabolism that is potentially subject to dietary and hormonal influence.

Fang and Strobel (1981) have demonstrated the control of carcinogen hydroxylation in rat colon by gastrointestinal hormones, and have accumulated evidence for the presence of multiple forms of cytochrome P-450 in colon microsomes.

Boffa et al. (1981a) have demonstrated that exposure of colon tumors to butyrate suppresses the malignant phenotype and leads to an expression of differentiated functions. Post-synthetic modification of chromosomal proteins represents a primary target of the butyrate action. In addition to inhibiting histone deacetylase activity directly, butyrate progressively but reversibly inhibits the phosphorylation of histones H1 and H2A. Other investigations on the role of the nucleolus and of ribosomal RNA in the control of cell proliferation are in progress (Baserga, 1981). Data presented by Augenlicht and Kobrin (1982) suggest that 1,2-dimethylhydrazine(DMH)-induced transformation of mouse colon cells is associated with extensive changes in gene expression.

Efforts have been directed at developing methods for the culture of human colonic carcinoma (Brattain et al. 1981a). The isolation of heterogenous malignant cell types with different biological properties from a single tumor has been described (Brattain et al. 1981b). Efforts are also directed at establishing epithelial cell cultures from normal human colon (CA 30185).

Detection, Early Diagnosis, and Prognosis of Large Bowel Cancer

Recognizing the importance of surface glycoproteins in the biological behavior of epithelial cells, Ahnen et al. (1982) demonstrated that CEA, normally localized to the microvillus surface, was diffusely distributed over colon cancer cells and that secretory component, normally localized to the basolateral surface, is diminished in amount or is absent in colon tumor cells. The data suggest that CEA or possibly other topographically restricted substances might serve as antigenic markers for the colonic microvillus surface.

The differential effects of sodium butyrate, dimethylsulfoxide (DMSO) and retinoic acid on membrane-associated antigens, enzymes, and glycoproteins of human rectal adenocarcinoma cells (HRT-18) has been investigated (Tsao et al. 1982).

Changes in the immunospecificity of nuclear antigens were demonstrated in the colon chromatin of rats treated with DMH. The level of nuclear antigen activity could be modulated in response to tumor promoters and inhibitors (Gabryelak et al. 1981). In related studies, the tumor-associated chromatin antigens of two human colon adenocarcinoma cell lines, HT29 and LoVo, were studied (Duhl et al. 1982). Antiserum immunoabsorbed with either LoVo or HT29 chromatin, failed to show any immunoreactivity, suggesting that the antigenic sites residing on these proteins are identical.

Considerable effort has been applied to the establishment of tissue cultures of human epithelial cells from benign colonic tumors (Friedman et al. 1981). The differential response of premalignant colonic epithelial cells to tumor promoters has been investigated (Friedman 1981).

In a continuing effort to identify high-risk individuals with hereditary colorectal cancer, the effects of TPA and EGF on proliferation of human mutant fibroblasts have been studied in vitro (Cansler and Kopelovich 1981). The results suggest that EGF and TPA may share only one class of receptors and that TPA may be used to monitor cancer progression. The suppression of tumorigenicity in human X mouse hybrids has

been reported by Chopan and Kopelovich (1981). The transformation-related traits expressed in the hybrid clones closely resembled the malignant mouse (A9) parental line. However, all hybrids displayed partial to complete suppression of tumorigenicity.

Diagnostic criteria for kindreds with familial polyposis coli and Gardner syndrome have been investigated at the cellular level. Chromosomes from individuals with these syndromes show excessive instability characterized by random structural and numerical aberrations. One member of the number 2 chromosome pair carries a consistent heteromorphism, tentatively identified as a deletion in the long arm at q14.3-21.3 (Gardner et al. 1982). Additional diagnostic criteria, in the form of extracolonic lesions that appear before adenomas in the colorectum, have also been described (Richards et al. 1981, Naylor and Gardner 1981). Further studies on the in vitro tetraploidy in heritable colon cancer syndromes have been conducted by Danes (1981) and in vitro evidence of genetic heterogeneity within the heritable colon cancer syndromes with polyposis have been more extensively studied (Danes and Alm 1981). Balis et al. (1981) continue to study enzyme variants of normal, premalignant, and malignant colonic cells.

As a part of an on-going study to detect early colon cancer, 21,961 individuals have been entered in a prospective controlled clinical trial to demonstrate the feasibility of screening for fecal occult blood in a standard risk, asymptomatic population over the past 6 years to detect colorectal cancers at an early (localized) stage, thereby increasing survival and reducing mortality. The program is unique in that it evaluates the benefit of both fecal occult blood testing and proctosigmoidoscopy as screening techniques. Follow-up continues in an effort to obtain reliable estimates of the incidence rates of colon/rectal cancers, survival rates, and total mortality due to colorectal cancer in the study and control groups (Winawer et al. 1982, Winawer and Fleisher 1982).

Using an orthotopic transplant of syngeneic murine adenocarcinoma cells (MCA-38), Raina et al. 1981 have observed that the dynamic changes detected by the Winn neutralization test parallel the alteration of specific antitumor immunity observed in vitro in the microplate leukocyte adherence inhibition assay. The selective loss of immunity in the local and regional compartments may play a permissive role in metastasis formation. Sjogren (1981) has found that administration of pure protein A to rats bearing colon cancer isografts inhibits tumor growth. He has observed that Cimetadine increases the natural killer (NK) cell activity in vitro and potentiates the interferon-induced activation of NK cells. The identification and characterization of the CEA-related antigen, TEX, has been described and a radioimmunoassay (RIA) specific for TEX has been developed (Shively et al. 1982). The nature of the carbohydrate determinants in CEA have been more clearly defined by developing a polyethylene glycol-based RIA (Pompecki et al. 1981a). Using this immunoassay, elevated levels of anti-Lewis antibodies in the sera of cancer patients have been demonstrated (Pompecki et al. 1981b).

Developmental and Clinical Therapy for Large Bowel Cancer

In conjunction with Dr. Hynes, who is synthesizing new folate analogs directed toward improved chemotherapy of colon adenocarcinoma (Yang et al. 1981, Hynes et al. 1982), Dr. Bertino is evaluating the effectiveness of this series of 2-amino-4- hydroxyquinazoline for activity against human colon cancer line HCT8 propagated in vitro. One compound, H338 (IAHQ), has shown good activity in this system and against a mouse colon adenocarcinoma (No. 38) (Fernandes et al. 1981). The data

suggest a new mechanism for its antitumor effect, namely the conversion of the analog intracellularly by polyglutamate synthetase to a potent inhibitor of thymidylate synthetase.

Using autochthonous tumors induced by a variety of colon carcinogens, it has been demonstrated that oral administration of indomethacin (20mg/L), a prostaglandin inhibitor, has antitumor or antipromotional activity and causes reductions in colon tumor incidence (Pollard and Luckert 1981a, 1981b). As the tumor burden was reduced by reducing the dosages of carcinogen, the efficacy of indomethacin therapy was increased. Peroxicam, a prostaglandin blocking agent with low toxicity, was equally inhibitory.

Using a transplantable murine colon tumor, T36, the selective inhibition of protein synthesis by sodium cyanate has been demonstrated (Allfrey et al. 1981) and its activation has been studied in culture (Boffa et al. 1981b). No inhibition of protein synthesis was observed in butyrate-treated tumor cells exposed to the cyanate/S9 system, whereas cells cultured in the absence of butyrate remained cyanate-sensitive (Boffa et al. 1981b). Using human colon carcinoma cell lines and their subclones, Leith et al. (1982) have demonstrated differential drug sensitivities as well as differential responses to x-irradiation and hyperthermia. Using several differentiation modulating agents, maturational effects on tumor cells have been noted. Several established colon carcinoma cell lines have been well characterized (Stragand et al. 1981) and their differential response to therapeutic agents has been evaluated as a function of cell differentiation and proliferative status (Drewinko et al. 1981, Drewinko and Barlogie 1982).

Biochemical determinants and responsiveness of particular tumors to specific agents and the mechanisms of tumor inhibition are being studied. The mechanism of tumor inhibition by alanosine, an aspartate analog which inhibits adenosine 5' -monophosphate synthesis, has been investigated (Hurlbert et al. 1982a). Studies to identify the biochemical determinants of responsiveness of 5-fluorouracil and its derivatives in human colorectal adenocarcinoma xenografts suggest that the response relates to the inhibition of thymidylate synthetase, and not to the level of incorporation of the triphosphate, or the frequency of its substitutions into total RNA at dose levels toxicologically acceptable to the host (Houghton et al. 1981). Preliminary studies of uridine kinase activity in human colorectal adenocarcinomas has been completed (Ahmed et al. 1981). The efficacy of the de novo synthesis of uridine 5' -monophosphate (UMP) is being studied in a large number of human neoplasms. The development and improvement of quantitative techniques for measuring treatment effectiveness on apparent or subclinical disease continues to receive emphasis.

Developing Resources

Synthetic bile acid reference standards are available to interested investigators (CA 21656). A cell bank of human and experimental colon tissue has been established at the ATCC to promote large bowel cancer research (CA 25635).

Emphases and Projections

A major emphasis has been on programs aimed at the prevention of large bowel cancer, with special emphasis on: 1) identifying and characterizing mutagens (potential carcinogens), 2) assessing "high-risk" populations and dietary factors believed to exert an influence on large bowel carcinogenesis; 3) developing immunopreventive approaches; and 4) studying drugs which may interfere with the

carcinogenic process.

Model systems, now well developed, are expected to expand our concepts and knowledge concerning large bowel cancer. Such models are now being used to: 1) identify and test new anticancer drugs, 2) identify potential inhibitors of carcinogenesis, 3) develop approaches to immunoprevention, 4) discern factors associated with transformation of colon epithelium to precancerous lesions and carcinoma of the large bowel, using molecular genetic approaches, and 5) assess the influence of dietary factors and the microflora in the initiation, promotion, or inhibition of large bowel cancer.

Methods derived from research in cellular biology will be utilized to ascertain alterations in cellular behavior and to identify phenotypic expressions characteristic of high-risk individuals. Identification of cellular and biochemical properties related to growth and metastatic potential of large bowel cancer will be encouraged. Programs in screening and early diagnosis of large bowel cancer will also be fostered with particular emphasis on evaluating the factors affecting their implementation and efficacy.

The National Large Bowel Cancer Project will foster development of new chemotherapeutic drugs to treat large bowel cancer. Research will be pursued to identify targets dealing with metabolic pathways involved in nucleic acid and protein synthesis. Cell surface glycoproteins and fundamental studies of membrane structure will be continued to uncover abnormal, exploitable, cellular functions.

Other Program Activities

The eighth workshop, "The Large Bowel Cancer Program: Its Achievements and Future Directions of Investigation", was published in The Cancer Bulletin, 33 (4), July-August, 1981. The revised annual Announcement of programmatic priorities was a result of the workshop. The NLBCP has co-sponsored a conference on "Prevention of Hereditary Large Bowel Cancer." A workshop on Markers of Colonic Cell Differentiation will be sponsored in the Fall at Southwest Harbor, Maine. The Proceedings of these workshops will be published.

The National Large Bowel Cancer Project and the American College of Surgeons jointly sponsor an exhibit on colorectal cancer entitled, "Large Bowel Cancer - Biology and Control". The exhibit has been updated, and has been shown at 27 meetings with 2,625 companion brochures having been circulated.

The activities of the National Large Bowel Cancer Project are publicized and distributed in a quarterly Newsletter and an annual Announcement.

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NATIONAL PANCREATIC CANCER PROJECT

The National Pancreatic Cancer Project (NPaCP) is an Organ Site Program established by the National Cancer Institute to stimulate research in the underdeveloped area of pancreatic cancer research. The Project began functioning in 1975 with its headquarters at the Louisiana State University Medical Center. Functions of the NPaCP include promotion and review of grants for pancreatic cancer research, dissemination of information to scientists, physicians, and the general public, and stimulation of scientific collaboration through conferences and workshops.

Pancreatic cancer is the fourth leading cause of death due to cancer and has the highest mortality to incidence ratio among major cancers. Due to the anatomic location of the pancreas and the relatively asymptomatic early stages, diagnosis of pancreatic cancer is extremely difficult. Treatment of pancreatic cancer also is hindered by the location of the pancreas and by the resistance of the disease toward conventional therapeutic regimes. While early diagnosis, effective treatment, and prevention are ultimate goals of the NPaCP, the current primary aim of the Project is to stimulate basic research which will lay the foundation for studies which will directly address the problems of pancreatic cancer.

Accomplishments

To date the NPaCP has reviewed 244 grant applications of which 75 have been funded. Now in its eighth year of operation, the Project is currently funding 32 research projects and eight others have been approved with recommendations for funding. In accordance with statements made in the above introduction, much of the work funded by the NPaCP is for basic research. This includes projects involved in experimental biology, carcinogenesis, pathology, epidemiology, immunology and tumor markers. While the clinical and applied fields of diagnosis and treatment are de-emphasized at present, important studies in these areas also are being funded. This emphasis on basic research is evident in the following summary of project accomplishments for the fiscal year of 1982.

Characterization of the normal pancreas has been conducted by DiMagno (CA 25064). It has been postulated that pancreatic cancer may result from reflux of carcinogenic agents from the duodenum into the bile duct. DiMagno et al have disproved this theory by showing that an efficient antireflux mechanism exists (Keane, 1981). Reflux is prevented by a sphincter at the opening of the pancreatic duct. In other experiments, these investigators have shown that physiological doses of nicotine shorten the cycle of interdigestive secretion and duodenal motility and, thus, increase duodenal motility and pancreatic secretion of trypsin and bicarbonate (Keane, in press). These effects of nicotine may be related to pancreatic cancer due to the positive correlation between cigarette smoking and pancreatic neoplasia. DiMagno et al also found that pancreatic secretion and duodenal motility in humans are cyclical and serve to clear the stomach of refluxed duodenal secretions (Keane, 1981).

The study of carcinogenesis has been a primary emphasis of the NPaCP. When the Project began in 1975, there were no acceptable animal models with which to study pancreatic cancer. Now that a number of good models are available, the Project has encouraged their characterization and use in innovative experimental studies.

Black (CA 16263), Gunther (CA 26561), Iqbal (CA 20914), Parsa (CA 22682), Pour (CA 20198) and Reddy (CA 23055) are among the investigators funded by the NPaCP to utilize these animal models for study of carcinogenesis (aspects of pancreatic neoplasia). A review of accomplishments in this field has been published by Reddy (Reddy, 1981).

Black et al have demonstrated that the rat pancreas responds with changes in DNA and RNA content to treatment (in vivo) with the pancreatic carcinogen 7, 12-dimethylbenz(A)anthracene (Black, in press). There appears to be a biphasic response with an initial depression of DNA, RNA and protein synthesis occurring from 2 to 16 hours post-treatment followed by an increase in DNA synthesis from 16 to 48 hours. While DNA replication was depressed during the first phase, repair synthesis was increased almost two-fold. RNA content in both nuclear and cytoplasmic compartments was significantly depressed at 5 and 22 hours. Additionally, the cytoplasmic content was depressed at 48 hours. These observations are consistent with findings in neoplastic tissues of other organs and with the theory of macromolecular control of the carcinogenic processes.

Gunther has examined the effects of the tumor promoting agent 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on calcium efflux in guinea pig phorbol acinar cells (Gunther, in press). Secretagogues such as caerulein (an analogue of CCK), carbamylcholine (cholinergic agonist) and calcium ionophore A23187 stimulate rapid release of calcium into the cytoplasm which triggers an increase in the level of cGMP and, by a separate series of events, protein discharge. In contrast, TPA appears to stimulate protein discharge independent of either increased cGMP or calcium discharge. This finding may help elucidate the physiological significance of the phorbol ester in normal acinar cell function, and its potential role in the etiology of pancreatic cancer.

Iqbal has been investigating the metabolism of nitrosamines in the Syrian hamster model of pancreatic cancer. Following injection of the pancreatic carcinogen N-nitrosobis(2-oxopropyl)amine (BOP), Iqbal et al found that the metabolite N-nitroso(2-hydroxypropyl) (2-oxopropyl)amine) (HPOP) has a higher concentration and a longer half-life in the pancreas than in other affected tissues (Whalley, 1981). N-nitrosobis(2-hydroxypropyl)amine (BHP), another important metabolite of BOP, was found in significantly smaller concentrations than HPOP in both the pancreas and plasma. These observations are consistent with the theory that HPOP is a more proximate carcinogen than BOP.

Parsa has produced the first in vitro model of pancreatic neoplasia. Carcinomas in organ cultures of human pancreas explants were induced by dimethylnitrosamine (DMNA) (Parsa, 1981). DMNA induced both ductal hyperplasia and atypia of the epithelial linings of main ducts, smaller ducts, and ductules within 6 weeks. Cells derived from 10-week-old DMNA-treated explants produced multiple nodules of carcinoma when injected subcutaneously into nude mice.

Pour et al have continued to characterize the Syrian hamster models of pancreatic cancer which they developed. As would be expected, DNA damage due to BOP was found to be greater in the pancreas than in the liver or salivary gland (Lawson, 1981). Furthermore, repair mechanisms in the pancreas, unlike those of other tissues, were not able to mend the damage caused by high concentrations of BOP. Differences in alkylation of BOP in target (pancreas) and non-target (liver) tissues were noted (Lawson, 1981). There are two alkylating agents in the liver, a methylating

agent and a 2-oxopropylating agent. The pancreas, however, appears to only methylate a one-carbon alkyl group. Following BOP injection, a potential methylating metabolite, N-nitrosomethyl (2-oxopropyl)amine (MOP) was identified in both the pancreas and liver (Lawson, 1981). The investigators also have identified several other carcinogenic agents in the hamster model; N-nitrosobis(2-oxobutyl) amine (BOB), N-nitroso(2-oxobutyl)(2-oxopropyl)amine (OBOP) and N-nitroso-2-methoxy-2,6-dimethylmorpholine (Pour, 1981).

Kim (CA 24321) and Yunis (CA 19182) have used in vitro techniques to study various biological aspects of pancreatic cancer. Kim et al demonstrated that three pancreatic cancer cell lines (PANC-1, CAPAN-1 and MIA-PaCa-2) attach to collagen in vitro (McIntyre, 1981). Anchorage independent growth, such as this , is the in vitro property which has been found to correlate best with tumor formation in vivo. Yunis et al have found that both Acinetobacter glutaminase-asparaginase and L-(αS, 5S)-α amino-3-chloro-4,5-dihydro-5-isoxozoleacetic acid (Acivicin) are effective inhibitors of MIA PaCa-2 cell growth (Meck, 1981 and Wu, in press). One mode of action for Acivicin appears to be a partially irreversible binding with gamma-glutamyl transpeptidase (Allen, in press). Yunis et al also have immunologically and functionally characterized colony stimulating factors I and II (Wu, 1981).

Using the tools of immunology, Chu (CA 18410) and Scheele (CA 22582) have identified pancreas-specific antigens and pancreas-associated proteins. Chu and co-workers have identified and characterized three different human pancreas-specific antigens and one human pancreatic cancer-associated antigen (PCAA) (Loor, 1981; Papsidero, in press and Tan, 1981). These antigens are now being used as potential markers for pancreatic cancer and for studies of pancreatic secretion. Chu et al also have established a human pancreatic tumor cell line, AsPC-1 (Chen, 1982). These cells also express PCAA. Novel approaches for protein isolation have been described by Chu and Scheele. Chu et al used isoelectric focusing of immune complexes bound to Protein A-Sepharose to separate IgG immunoglobulins from human biological fluids (Maidment, 1981). Scheele et al identified 15 discrete proteins from human pancreatic juice by two-dimensional isoelectric focusing/sodium dodecyl sulfate gel electrophoresis (Scheele, 1981).

Danes (CA 25662), Goodale (CA 20115), Hubner (CA 29490) and Rinderknecht (CA 20222) have been investigating possible avenues of early diagnosis. Since diagnosis of pancreatic cancer could be enhanced by the identification of risk factors, Danes is studying the possibility of genetic risk (Danes, 1981). Initial findings indicate that a small genetic risk may exist and that this risk may be identified by hyperploidy in monolayer dermal cultures (Danes, in press). Goodale et al found that endoscopic retrograde cholangiopancreatography was 80% effective in diagnosing symptomatic patients with pancreatic cancer (Goodale, 1981). The investigators also found that pancreatic secretions from cancer patients had a 10-fold greater concentration of albumin, 2- to 7-fold greater IgG concentration and a 6- to 15-fold greater concentration of IgA than secretions from patients with pancreatitis. Hubner et al have described the diagnostic method of positron emission tomography (Hubner, in press). Rinderknecht has described a method of diagnosing pancreatic disease by fluorometric determination of plasma trypsinogen (Rinderknecht, in press).

Treatment protocols have been described by Dobelbower (CA 25733) and Goldson (CA 26658). Dobelbower et al have used a combination of ^{125}I-implantation and

precision high-dose (PHD) external beam radiotherapy for treating patients with non-resectable pancreatic carcinoma (Whittington, 1981). This regime has a median survival of 10½ months and appears to be more effective than PHD alone. Goldson is using intraoperative radiotherapy (IOR) for treatment of pancreatic carcinoma (Goldson, 1981). Clinical data suggest that pre-operative percutaneous biliary decompression and hyperalimentation improve patient tolerance and hasten surgical recovery. The median survival for these patients, 80% of whom had distant disease, was six months.

Gold (CA 29489) and Longnecker (CA 19410) also have published data supported by the NPaCP. Gold et al found that human colonic adenocarcinomas produce an alpha-1-proteinase inhibitor which is capable of inhibiting pancreatic elastase (Lee, in press). Longnecker et al found that islet amyloid occurs in 12% of nondiabetics, in 59% of diabetics, and in 89% of diabetics undergoing insulin treatment (Maloy, 1981).

Other Program Activities

In addition to supporting the research discussed in the Accomplishments section, the NPaCP has stimulated interest, collaboration and research in the field of pancreatic cancer through Project supported literature and meetings. During the past year the NPaCP has published the proceedings of the International Union Against Cancer Workshop on Pancreatic Cancer (Cohn, 1981), the proceedings of the Workshop on Radiation Therapy (Cohn, 1981), proceedings of the Workshop on Pancreatic Tumor Markers (Kupchik, 1982), and an overview of pancreatic cancer (Beazley, 1981). The NPaCP has also published its biannual Newsletter which has a circulation of approximately 1100 readers, and the abstracts of the 1981 NPaCP-APA (American Pancreatic Association) meeting. The NPaCP-APA meeting featured 37 presentations on various aspects of pancreatic cancer including a keynote speech by Dr. Brian McMahon on risk factors. In March of 1982 the NPaCP sponsored an Epidemiology Workshop at NCI. Approximately 50 experts attended this meeting to discuss the volatile issues of methodological problems in pancreatic cancer epidemiology, current epidemiological findings and their etiological relevance. Results from the two largest case-control studies along with those of smaller case-control studies and preliminary results of prospective cohort studies implicate a triad of risk factors in the etiology of pancreatic cancer; tobacco, alcohol and coffee. In April of 1982 the NPaCP held a symposium entitled "Experimental Approaches to Pancreatic Cancer Research: Transformation in Acinar Cell Surface Properties" in conjunction with the meetings of the Federation of American Societies for Experimental Biology. Talks by headquarters staff and grantees focused on basic cellular transformations occurring in pancreatic carcinogenesis. These presentations were used to highlight questions facing the field of pancreatic cancer which could be addressed by basic researchers. This was the first attempt that has been made to open avenues which could lead basic researchers into this field. Other activities conducted by the Project include three meetings of the NPaCP Subcommittee to review grants and establish priorities, and numerous presentations by the Principle Investigator, Dr. Cohn, on the topic of pancreatic cancer. These publications, conferences, and workshops in addition to the scientific research sponsored by the NPaCP have had an impact on the field of pancreatic cancer and it is expected that future work by the NPaCP will be of the same value.

Emphases and Projections

The immediate goals of the NPaCP are to generate research which will result in a better understanding of the pancreas and the basic nature of pancreatic cancer. There are three major reasons for the Project's emphasis on basic research. First, the unique problems presented by pancreatic cancer and the lack of basic information dictate the need for more fundamental knowledge. Secondly, there is a lack of investigators in this aspect of research. The third reason is that there are attractive avenues for funding of clinical projects whereas there are limited resources for basic experimentation. This is evidenced by the $2.86 million spent by NCI on clinical contracts for the study of pancreatic cancer as compared to the $0.95 million spent on basic research (R01). Thus, the NPaCP has filled and will continue to fill this vacuum. Innovative experimentation, characterization of cancer models, and the development of tumor markers and biological probes will be stressed. To aid in these endeavors the NPaCP plans to establish a specimen and cell bank which will allow investigators easier access to materials needed for study. It is expected that such an easy access to samples in addition to the availability of research models will encourage more investigators to study pancreatic cancer. The Project also will continue to sponsor conferences and workshops, publish literature for the scientific community, encourage collaboration and stimulate interest in the field of pancreatic cancer.

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NATIONAL PROSTATIC CANCER PROJECT

The National Prostatic Cancer Project (NPCP), initiated in 1972, represents an integrated effort in wh ch the planning, coordination, and scientific administration of its programs are conducted at the Project Headquarters located at Roswell Park Memorial Institute, under the direction of Dr. Gerald P. Murphy. The overall strategy of the NPCP has been to share major responsibilities between the National Cancer Institute and scientists throughout the nation for development and implementation of a program aimed at prevention and decreased mortality due to prostate cancer. This involves a multidisciplinary research program which addresses high priority projects that have been identified by the scientific and clinical community. The major result toward which these studies are providing progress is measured in terms of increased survival time and delay in the development of progressive disease.

On a continual basis, and in concert with annual planning meetings of the Working Cadre, new areas in need of research are identified and publicized as a mechanism for attracting grant applications into targeted and high priority areas relevant to prostate cancer. The NPCP continued to investigate and implement programs and strategies for experimental and clinical research which, based on the evaluation and analysis of current knowledge and information, offered the best opportunities for immediate and visible success at all levels of endeavor.

Accomplishments

Significant accomplishments were reported during the current period in the Etiology/Prevention, Detection/Diagnosis and Treatment categories of NPCP research grant activity.

Etiology/Prevention

Greater emphasis has been focused on the causal and preventive factors related to prostate cancer, particularly in the fields of nutrition and chemoprevention e.g. retinoids. Of particular note is a new epidemiologic study in progress at the University of Hawaii which will compare cases of prostatic cancer and controls on selected dietary components (fats, vitamin A, vitamin A precursors, and zinc-to-cadmium ratio). Cases are identified through seven major hospitals on Oahu, Hawaii, and controls matched on age and sex are selected by a random-digit procedure. Quantitative dietary histories, from which nutrient intakes can be assessed, are administered to all subjects. During the past year, interviews were completed on 205 cases and 224 controls. Food composition data includes all of the foods and nutrients particular to this study. Analysis of the case-control data will be carried out during the next year, after interviews are completed on a projected 400 cases and 800 controls. At Howard University, investigators are examining whether dietary and/or lifestyle habits of American black males are related to the high incidence of prostatic cancer. Thus far, a total of 163 patients have been enrolled in this study. In the nutritional portion of the study the observations suggested that patients ate more yellow vegetables than controls, and that prostate cancer patients from ages 30-49 consumed less fruit juices.

Animal models for studies of prostate cancer have been developed by investigators supported by the NPCP. Their use in furthering our understanding of basic mechanisms involved with prostate cancer and metastasis have led to some important findings (Coffey, Isaacs 1981; Isaacs et al, 1981). For example, investigations

of several distinct sublines developed from the original Dunning rat prostatic R-3327-H tumor suggests that acquisition of some characteristics by the tumors represents a process of tumor progression into fully developed malignancies (Isaacs et al, 1981). Comparison of chromosomal changes and characteristics observed in the tumors suggested that the growth rate, dedifferentiation and attainment of metastatic ability were related to chromosome variation (Wake et al, 1982). These results point to the importance of chromosome changes in the early development of tumors (Sandberg 1981). Studies of defined human populations have clearly shown a familial association with prostatic cancer (Meikle, Stanish 1981) further suggesting genetic involvement.

Other investigators have made discoveries in animal prostate that may lead ultimately to further understanding and applications to the normal human prostate and the disease (Pollard, et al 1981). Alpha-protein has been identified as a non-receptor steroid-binding protein in the rat ventral prostate which could, in vitro, inhibit the association of an androgen-receptor complex with nuclear chromatin (Liao, et al 1981). This protein is a major secretory protein in the prostate, which can be used as an excellent specific marker for rat prostate with possible applications, ultimately, to the human. Progress has been reported in the use of established in vitro human prostatic adenocarcinoma cells as a new model in nude mice for studies on etiology, biology, detection and therapy of human prostatic neoplasia (Horoszewicz, et al 1982). This is clearly a valuable model which closely resembles human prostate cancer.

Detection/Diagnosis

During the current year, there has been further characterization of established markers for human prostate (Anderson, et al 1981; Bolton, et al 1981; Catalona, Menon 1981). Moreover, significant results have been obtained from the following areas of investigation on the human prostate-specific antigen (PA): biochemical characterization of PA, identification of PA isoantigens, clinical evaluation of PA (alone and in combination with prostatic acid phosphatase, PAP), generation of hybridoma-derived monoclonal antibodies to PA and in vivo radioimmunodetection of prostate carcinoma xenograft with the use of PA xenoantibodies (Nadji, et al 1981; Papsidero, et al 1981). Serologic evaluation of PA has revealed that pretreatment level of PA is of prognostic value in regards to patients' survival (Kuriyama, et al 1981). Serial PA levels also are of value in early detection of disease recurrence and monitoring of treatment response (Nadji, et al 1981). Simultaneous determination of PA and PAP has demonstrated an additive clinical value of PA and PAP in various stages of prostate cancer.

The need for non-invasive means of diagnosing prostate cancer has resulted in specific applications of bone scans for prostatic cancer response criteria (Pollen, et al 1981). Another study on prostatic fluid subjected to analysis for a variety of substances was undertaken in an effort to identify changes that would differentiate individuals with a high risk of carcinoma of the prostate from patients with benign prostatic hyperplasia, inflammatory disease of the prostate, and normal males (Grayhack, Lee 1981). Among the compounds studied the lactic dehydrogenase (LDH) isoenzymes, the C_3 component of complement, and transferrin had demonstrated alterations in concentration in patients with carcinoma.

Each year studies of steroid hormone receptors in human prostate specimens bring this technology closer to actually being of value in predicting which cancers will respond to hormonal therapy (MacLaughlin, et al 1981; Mobbs, et al 1981; Pertschuk, et al 1982). Reliable and specific assays have been developed for the characterization and quantitation of androgen receptors in the cytosol and

soluble KCl extracts of nuclei prepared from human prostatic tissue (Trachenberg, et al 1982). The measurement of nuclear resistant receptors may improve, as suggested by some clinical studies, the usefulness of receptor levels to predict the hormonal responsiveness of prostatic cancer (Trachenberg, Walsh 1982). Moreover, it was recently reported that estrogen receptors, when detected in prostate cancer specimens, may play a significant role in identifying a subset of hormonally sensitive tumors with a specific histologic tumor grade (Pontes, et al 1982).

Other studies for markers for prostate cancer have suggested that tissue levels of dihydrotestosterone in Stage D_2 prostate cancer patients may be useful for predicting the clinical response of prostate cancer to anti-androgen therapy (Geller, et al 1981; Geller, et al 1981). Additional support for this conclusion must await further follow-up of additional patients entered into the study with dihydrotestosterone levels less than 2.0 ng/gm.

Treatment

The Cooperative Clinical Trials Program of the NPCP have established that favorable responses and acceptable degrees of toxicity can be obtained with cytotoxic treatment and that chemotherapy can be recommended as a legitimate option for patients with endocrine-resistant prostatic carcinoma (Murphy, et al 1982). Presently, while there is a continued effort to evaluate single agent drug therapy, additional studies are in progress to evaluate combinations of agents that have proved effective. Also, adjuvant chemotherapy protocols for earlier stages of cancer and adjuvant therapy to surgery or irradiation have been added to the studies. Ten studies have been completed in terms of patient accrual but surviving patients are still being followed and evaluated. The results to date warrant the following conclusions (Loening, et al 1982; Loening, et al 1982; Murphy, et al 1982; Soloway, et al 1982; Soloway, et al 1982): 1) On the basis of both objective and subjective criteria, chemotherapy has demonstrated advantage over conventional therapy in hormonally resistant advanced Stage D disease; 2) Patients who respond to chemotherapy survive significantly longer than non-responders; 3) In patients with advanced disease, objective partial regressions were only observed in those treated with chemotherapy; 4) Active single agents with acceptable and manageable side effects are Cytoxan, 5-FU, Estracyt, DTIC, Methotrexate, cis-Platinum and Streptozotocin. Minimal activity and excessive side effects were observed for Hydroxyurea, MethylCCNU and Procarbazine. Vincristine and Leo 1031 alone exhibited minimal activity and in combination with Estracyt did not improve response or survival over either agents alone. The combination of cis-Platinum and Estracyt was superior to either agent used alone; 5) In patients with previously untreated advanced disease there is evidence that adding chemotherapy to hormones for the initial treatment is advantageous, particularly for patients with symptoms of pain.

The NPCP is currently conducting chemotherapy trials for several types of disease, including 1) Advanced disease (Stage D_2) that is refractory to hormones (at least orchiectomy) and has not been treated with radiotherapy (<2000 rads to pelvis) or chemotherapy; 2) Advanced disease (Stage D_2) that is refractory to hormones (at least orchiectomy) and has been treated with radiotherapy (<2000 rads to pelvis) or chemotherapy; 3) Newly diagnosed and untreated advanced disease (Stage D_2); 4) Advanced disease (Stage D_2) that is stable to orchiectomy or estrogenic hormone treatment; 5) Non-metastatic disease, Stage B_2-D_1 treated definitively with a prostatectomy plus pelvic lymph node resection followed by adjuvant chemotherapy; 6) Non-metastatic disease, Stages B_2-D_1 treated definitively with external or internal radiotherapy plus pelvic lymph node resection followed by adjuvant

chemotherapy; 7) Patients with Stage A_2 disease with negative lymph nodes will receive definitive surgery or external radiotherapy. In addition to these, two protocols have been recently activated to 1) survey patients with Stage A_1 prostate carcinoma and to 2) conduct a comparison of definitive therapies, surgery versus external irradiation, for Stage A_2 prostate adenocarcinoma. Over 2100 patients have now been admitted to these protocols.

Studies related to treatment of prostate cancer have involved the synthesis and testing of various agents with potential activity against prostate cancer (Batzold 1981; Petrow, et al 1981; Sandberg 1981). A study of androgen sensitive tumors in the Noble rat confirmed previous laboratory data by revealing that chemotherapy plus castration decreased both tumor volume and number of metastases more than in the castrated only groups (Drago, et al 1981).

Emphasis and Projections

The NPCP continues to investigate and implement programs and strategies for experimental and clinical research which, based on the evaluation and analysis of current knowledge and information, will offer the best opportunities for immediate and visible success at all levels of endeavor. In the Etiology/Prevention area, studies will focus on experimental biology and epidemiology of prostate cancer. Many of these studies will utilize animal tumor models and human prostate specimens provided by the NPCP. Particular emphasis will be placed on both nutritional and chemopreventive aspects of prostate cancer. Areas of priority are: identification of risk factors and prevention approaches in populations with differing risks of prostatic cancer; environment and occupational factors which affect the development of prostatic cancer; development and aging of the prostate: role in prostatic cancer; role of cellular and intrinsic factors in prostatic carcinogenesis; analysis of prostatic fluid for determination of acinar cell milieu and the detection of carcinogens, biological markers and promoters of prostate cancer; trace metals in prostatic cancer; cytogenetic factors in prostate cancer; further characterization of hormone receptors, steroid levels and enzyme profiles in normal, BPH and cancerous prostatic tissue; endocrine alteration associated with the development of prostatic cancer; role of peptide hormones in growth regulation of normal and malignant prostatic epithelium; growth and maintenance of normal, benign and malignant human prostatic epithelium *in vitro*; genetic regulation and expression in prostatic cancer; the progression of prostatic cancer and the development of metastasis; prostatic binding systems for substances other than hormones (polyamines, prostaglandins, drugs); the availability of animal models for the study of prevention, initiation and modulation of prostate cancer; the surface of normal and malignant prostatic cells; subcellular alterations in prostate carcinoma; and interaction between stroma and epithelium of the normal and neoplastic prostate gland.

In the Detection/Diagnosis area, studies dealing with earlier detection and more accurate diagnosis of the stage (clinical and pathological) of prostate cancer, and the response to therapy are being emphasized. Many of these studies will involve new techniques that have evolved from basic advances in tumor immunology. In addition, research aimed at improving the precision of predicting the biological potential of both newly diagnosed tumors and those undergoing therapy will be implemented. Priority areas for the upcoming year are: biochemical and other markers for detection of patients with prostatic cancer; evaluation of non-invasive imaging techniques for the detection of prostatic cancer; development of radioisotope agents for detection and staging of metastatic prostate cancer; morphologic

definition of lesions associated with and precursor to the development and progression of adenocarcinoma of the prostate; evaluation of the use of histochemical techniques for the localization of receptors and other binding proteins in the prostate gland; comparison of new analytical methods of prostate cancer detection; cytogenetics of prostate cancer; human hybridoma to prostatic carcinoma; and kinetics of prostatic carcinoma.

In the Treatment area, the NPCP has defined among its objectives 1) the evaluation and improvement of additional therapy modalities on prostatic cancer by testing and selection of new agents and procedures, and the determination of their therapeutic effectiveness, and 2) the development of combination therapeutic modalities where appropriate, based upon new information, and the evaluation of their usefulness in clinical disease states involving local, regional, and metastatic disease. Emphasis continues to be placed on: evaluation and comparison of therapeutic modalities for prostatic cancer; clinical demonstration studies of newer treatment approaches in nodes positive and/or high grade histopathology (Gleason staging 7, 8, 9, & 10) prostate cancer; evaluation of nutritional status and nutritional intervention in advanced prostatic cancer; the development and evaluation of new concepts to control prostatic growth; studies on the development of resistance and tumor cell heterogeneity in prostatic cancer; and biology of invasiveness and metastatic spread in prostate cancer. Increasing both survival time and time to development of progressive disease, as well as obtaining objective and subjective responses in prostatic cancer, are major goals.

Other Program Activities

Periodically, the NPCP identifies topics of growing investigational activity and importance in prostatic cancer. In response, authorities are called on to review the pertinent subjects and to provide direction for future programmatic implementation and impact. On March 8-9, 1982, at Roswell Park Memorial Institute, over 30 investigators participated in an assessment of the current status of the histopathology of prostate cancer. Recently, the NPCP sponsored part of the faculty for the subject oriented seminar of the American Urological Association entitled "Clinical Status of Prostatic Carcinoma", held in Washington, D.C. on April 1-3, 1982.

The NPCP has continued to inform the scientific community of its activities by means of a quarterly Prostatic Cancer Newsletter that describes the Project's activities and publishes brief summaries of continuing research progress by investigators receiving support through this Project. Over 8,700 copies of five issues of the newsletter have been distributed nationally and abroad during the year to a readership of over 2,500 individuals. The NPCP Reprint File has been enlarged to over 5,000 reprints of articles on and related to the prostate, and is catalogued on the computer of the Central Statistical Office. Over 600 of the articles are by investigators supported through the NPCP. The Reprint File has been, and is proving to be a valuable resource for investigators and Working Cadre members.

Through programs supported by the NPCP, investigators are supplied with sera from prostate cancer patients, human prostate tissues and cultures, and R3327 tumor bearing rats. These have proven to be highly valuable resources for research projects which might not otherwise have been implemented had they not existed. These programs characterize the unique capability of the NPCP to both support and respond to investigators conducting research on prostate cancer.

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RESEARCH FACILITIES BRANCH

Objectives

The Cancer Construction Program's objectives are to support the National Cancer Program by assisting the extramural research effort in the following ways:

a. support new facilities to house cancer research activities including basic, applied, and clinical research;

b. upgrade existing research laboratories;

c. upgrade existing animal research facilities to comply with current DHHS criteria for animal care and employee safety;

d. upgrade clinical areas for applied cancer research;

e. provide biohazard containment units;

f. provide advice concerning biohazard safety and facility modifications to cancer researchers; and

g. provide advice to other NIH institutes concerning their research facility improvement programs.

Accomplishments

The NCI Construction Program continues to accomplish its stated goals. In the years since 1972 much has been accomplished; however, recent budget priorities have reduced the Construction Program to a smaller segment of the NCI's overall budget. The program provides grant support which requires that the grantee institution match the NCI-funding with an equal amount of non-Federal funding.

In FY 82, seven construction applications were received by NCI; they requested a total NCI-funding of $5,644,000. After a thorough evaluation by the peer review system, seven applications were recommended for approval and four were recommended with strong enthusiasm; total recommended NCI funding = $2,006,000. The available NCI Construction Program's funding of $1,225,000 was awarded to four of these institutions for renovation type projects involving the upgrading of existing cancer research laboratories.

CONSTRUCTION PROGRAM'S ACHIEVEMENT RECORD (1972-1982)

Goal	Achievements (No. of Projects) 1972-1981	1982
a. Build new cancer research buildings	44	0
b. Upgrade existing laboratories	20	4
c. Upgrade existing animal facilities	9	0
d. Upgrade clinical research facilities	8	0
e. Provide biohazard containment units	19	0
f. Provide technical advice to NCI	continuing	continuing
g. Provide technical advice to NIH	continuing	continuing

Projections

The earlier emphasis on the construction of cancer research buildings has changed to the renovation and upgrading of existing laboratories and animal facilities. The currently available annual funding of $1,250,000 has been awarded to renovation projects which are clearly justified on the basis of high quality scientific research, cancer relevance, and need for facility improvements.

Funding by Program Activities

In FY 82, four construction grants were awarded. Each of these grants was for the renovation of existing cancer research laboratories to upgrade the effectiveness of their research efforts and to improve the safety of the laboratory.

A summary of each of the FY 82 grants is given below:

1. University of Washington (1 C06 CA32596-01)
The University of Washington was awarded $220,000 in partial support of minor renovations to existing space in the Department of Biological Structure. The NCI funding was matched by $220,000 in University of Washington funding. The remodeled space accomodated the expansion of the cell differentiation and cellular immunohematology programs which were focused on the role of bone marrow derived cells in tumor resistance. A pathogen-free animal facility was included in the renovation project.

2. University of North Carolina (1 C06 CA32623-01)
The University of North Carolina School of Medicine was awarded $219,010 in partial support of the completion of research laboratories in their new Lineberger Cancer Research Building. The NCI funding was matched by $219,010 by the University of North Carolina.

The remodeled space was for the Virology and Cancer Cell Biology programs. The virology program had strong emphasis on molecular biology, human cytomegalovirus, and DNA-protein complexes. The cancer cell biology program is focused on the regulation of the mammalian cell cycle and tumorogenic retroviruses.

3. Albert Einstein School of Medicine (1 C06 CA32573-01)
Albert Einstein College of Medicine was awarded $639,785 in partial support of major renovations to the Leo Forchheimer Medical Science Building. The NCI-funding was matched by $639,785 in Albert Einstein College of Medicine funding.

The cancer research performed in the renovated spaces included the following areas: carcinogenic and chemotherapeutic agents; immunology; nucleic acid synthesis and viral oncology; membrane synthesis, structure, and function; gene expression in malignant cells; cell structure, function and regulation.

4. Boston University (1 C06 CA32573-01)
The Hubert H. Humphrey Cancer Research Center was awarded $146,205 in partial support of renovations. The NCI-funding was matched by $359,020 in Boston University funding.

The cancer research performed in the renovated spaces included the following research areas: DNA replication and control; biology of the tumor cell; and tumor immunology.

Staff Publications

Brow, K. Description of Biohazard and Other Containment Facilities. U.S. Department of Health and Human Services, Public Health Service. Bethesda, Maryland, National Institutes of Health, 1981, 137 pp.

Brow, K.: Laboratory Design. In 1982 Handbook: Applications. New York, American Society of Heating, Refrigerating and Air Conditioning Engineers, Inc., 1982, pp. 14.1-14.18.

Fox, D. The Cancer Construction Program - Program Instructions. U.S. Department of Health and Human Services, Public Health Service. Bethesda, Maryland, National Institutes of Health, 1981, 137 pp.

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IV.

EDUCATION PROGRAM

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CANCER COMMUNICATIONS NETWORK

The Cancer Communications Network (CCN) was established in 1976 for the purpose of assuring that accurate, up-to-date information on cancer cause, prevention, early detection, diagnosis, treatment, rehabilitation and continuing care is readily available and accessible to the public and health professionals. The CCN contracts were recently recompeted for an additional three years of funding and currently consist of 18 regional offices funded by NCI (Nos. 95471, 25566, 25567, 25568, 25569, 25570, 25571, 25572, 25573, 25574, 25575, 25576, 25577, 25578, 25579, 25580, 25581, and 25582). Three additional offices receive no funds from NCI but actively participate in the information exchange that occurs throughout the network.

Each network office is responsible for:

1. Establishing a Communications Office to plan, administer, promote, develop support materials for, and evaluate activities undertaken by the contract staff;

2. Developing and maintaining a resource directory of agencies and services available to cancer patients and their families within the defined service area of the center;

3. Establishing and operating a toll-free telephone service (The Cancer Information Service or CIS) for immediate access to answers on cancer-related questions from the public; and

4. Identifying, developing, implementing and evaluating a limited number of special projects to meet specific cancer information/education needs within the service area.

While the basic conceptual nature of the CCN program has not changed as a result of the recent procurement, some differences are evident in the new contracts. The new workscope represents program requirements in a more detailed fashion, provides for standardization among network offices in several areas, increases the NCI management role, and stresses the importance of quality control and evaluation. In addition, Special Project requirements have become more targeted, thus reducing to forty-four the number of Special Projects in which the network is involved.

Work continued on the national evaluation of the Cancer Information Service portion of the networks' operations. The quality assessment program has undergone pretesting, and the standardized call record form will be pretested soon.

The National Publicity and Promotion Task Force continued to advise NCI on promotional materials developed for the network. Revisions on the National Plan for Publicity and Promotion of the Cancer Information Service were completed. That document is now used as background and guidance for the network and for NCI. The task force is currently undertaking the development of a marketing plan for the Cancer Information Service, which will be completed in the next fiscal year. Two public service announcements (PSA's) were developed for the network by NCI, one of these in conjunction with the Decade of Discovery program. This PSA was co-sponsored by the Candlelighter's Foundation, Inc. It is currently a finalist

in a national competition for public service announcements. Other PSA's produced by various CIS offices, were replicated by NCI for use by the entire network.

The Staff and Volunteer Training Task Force has been established to develop a uniform staff and volunteer training program for use by the network. This task force will review all training programs currently in operation and use this information, coupled with new information, to develop a standard program.

At the end of this fiscal year, over 800,000 callers have been served by the Cancer Information Service since its inception. The CIS currently averages 11,500 calls each month, with over 135,000 total calls. Examples of Special Projects currently underway throughout the network include a series of leaders forums, Seniors Team Up Against Cancer health education project, A PAP smear education program for high risk women, cancer risk self-assessments, a cancer program for older citizens, cancer education programs targeted towards the Black and Hispanic community, an information dissemination campaign for rural audiences, and many newsletters, radio programs, and mass media campaigns providing cancer information and education to various target audiences. In addition, a Psychosocial Cancer Counseling Line (PCCL) has been developed by one office to meet the psychological and emotional needs of cancer patients and their families.

STAFF

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RESEARCH MANPOWER BRANCH

Overview

Objectives

The primary function and objective of the Research Manpower Branch is to provide, plan, organize and support a concentrated effort for quality research training and development for fellows and trainees ranging from the predoctoral level to the nearly-established investigator. Experience can be gained in applied and/or basic science areas. The branch also manages the cancer clinical education program which provides continuing education for health professionals and cancer curriculum improvement for medical students and others.

Accomplishments

In fiscal year 1980 under the Institutional Training Grants (T32) 518 predoctorals 707 postdoctorals (including 180 M.D.s) received training. The Individual Postdoctoral Fellowship Program supported 216 postdoctorals including 22 M.D.s. In addition, two short courses were held on the Pathobiology of Cancer, one in Keystone, Colorado the other in Lake Placid, New York. Research trainees and fellows lacking previous training in the actual disease mechanisms of cancer actively participated in these courses. In the case of the Cancer Clinical Education Program, 91 institutions received awards, including schools of medicine, dentistry and public health and specialized cancer institutions.

Program Projections

In 1982-83 the Research Manpower Branch proposes to do the following things: a) continue the development of the nutrition training grant effort which was begun in 1982; b) rethink the objectives of the Cancer Clinical Education Program; c) plan a new award of the Career (K) series designed to stimulate recruitment of more physicians into research, especially surgical oncologists; d) stimulate additional training applications in prevention and epidemiology.

Funding by Program Activities in FY 1982

Program	Number of Grants	Amount (millions)
National Research Service Awards		
Institutional	168	$19.2
Individual	165	2.9
Research Career Development Awards	106	4.1
Research Career Award Program	5	.16
Clinical Cancer Education Program	74	5.1
Contracts - Preventive Education	13	1.4
Veterinary Pathology Program	2	.29

Examples of Research Accomplishments by NRSA Trainees, Fellows and Research Career Development Awardees

At Yale University postdoctoral trainee Alexander Waldrop, has applied for a patent for "Modified Nucleotides and Method of Preparing and Using Same." This invention is expected to be of immense value in diagnosing infectious and genetic disorders. It will also be an invaluable research tool in nucleic acid sequencing and gene isolation procedures.

Dr. William Pearson at Johns Hopkins has shown that butylhydroxyanisole potentially increases the production of glutathione S-transferase (GST) in mouse liver 25 fold. GSTs are drug-detoxifying enzymes which protects animals against chemical carcinogens.

Dr. James Griffin working at the Sidney Farber Cancer Institute is defining the cell surface antigens of normal and malignant myeloid cells. He has developed a panel of monoclonal antibodies which recognize differentiation-linked markers of human myeloid cells. These are being used to define subsets of human acute nonlymphocytic leukemias. It is hoped that these efforts eventually will lead to clinical correlations such as those which already have been so useful in understanding acute lymphocytic leukemia.

S. Schwarzbaum is developing techniques for natural killer cell (NK) purification so that their characteristics may be studied. NK cells in humans are mononuclear cells which occur in peripheral blood and which are cytotoxic for certain tumor cells. Because NK cells comprise less than one percent of the total peripheral blood mononuclear cells, their study has been inhibited. Differential density gradient centrifugation techniques have been used to concentrate NK cells. Hybridoma techniques have been used to secure monoclonal antibodies which appear to be NK specific determinants. These antibodies are being used to further purify NK effector cells so that their structure and activity may be better defined. This work is being conducted at Albert Einstein College of Medicine.

Dr. Samuel Ahn is studying the first trial of immunization of human beings specifically directed against a characterized tumor-associated antigen. Oncolofetal antigen (OFA) is present in 80 percent of melanoma biopsy specimens. IgM antibodies directed against OFA produce in vitro lysis of melanoma cells in the presence of complement. After preliminary studies showed that patients who developed a strongly elevated IgM anti-OFA titer after immunization had a lengthy disease-free interval, studies were begun in Stage III melanoma patients. Because OFA is present in several other neoplasms, a successful vaccine would have potential use in those cancers also. These studies are being conducted at the University of California in Los Angeles.

At the M.D. Anderson Hospital and Tumor Institute, Dr. John Knapp has been studying the utility of cis-diamine-dichloroplatinum II (CDP) in malignant solid tumors. In a pilot study, four previously treated pediatric patients with unresected primary tumors were studied. CDP was administered intra-arterially via the major artery feeding the primary tumor. Treatment was administered at intervals of about two weeks for two to four courses. The primary tumor in all four patients responded clinically with more than 70 percent tumor destruction in two patients and less than 40 percent in the remaining two. Pulmonary

metastases were nonresponsive. A more definitive study has begun. Where tumor destruction is more than 60 percent, the concentration of CDP in the tumor is 17-40 micrograms/gram dry weight. With destruction of less than 60 percent, CDP measures 12 micrograms or less.

Activities by Program Areas

The Research Manpower Branch is responsible for the following programs: National Research Service Awards; (including research training grants and research fellowships) Research Career Development Awards; Clinical Cancer Education Grants and Contracts; and Short-Term Training.

NRSA-Research Training Grants

These institutional grants provide universities an opportunity to develop or enhance research training at the predoctoral and/or postdoctoral level. The applicant must have the staff and facilities for the proposed program. After the award is made, the institution's training program director has the responsibility for selection and evaluation of trainees. The administration of the institutional training grant is handled by the program director at the institution. Predoctoral students may receive up to eight years of support (five years as a predoctoral and three years as a postdoctoral) under the National Research Service Act (NRSA). The stipend for predoctorals is $5,040. Postdoctoral stipends depend on experience and range from $13,380 to $18,760. Postdoctoral candidates are limited to a maximum of three years of support under NRSA.

	Number of Grants	Trainees Pre	Trainees Post
Cancer Biology	17	36	87
Etiology & Prevention	94	459	456
Detection & Diagnosis	26	54	80
Treatment & Restorative Care	31	6	148
TOTAL	168	555	771

NRSA Research Fellowships and Other Individual Awards

The Individual Postdoctoral Fellowship Program provides the opportunity for those who have attained the research doctorate or a professional degree to broaden their scientific background. Applications are received in the same disciplines as the Institutional Training Grants. The postdoctoral fellow

receives the same stipend level as a postdoctoral trainee. An applicant for a postdoctoral fellowship must establish his acceptance by a preceptor and must present a detailed description of the research project which he will undertake as part of his research training. The individual fellow is limited to three years of support. A senior postdoctoral fellowship is available to faculty members and others having more than seven years postdoctoral experience.

	Number Awarded
Cancer Etiology & Prevention	129
Cancer Detection & Diagnosis	4
Cancer Treatment & Restorative Care	73
TOTAL	206

Research Career Development Awards

The purpose of the Research Career Development Awards is to provide very promising young investigators the opportunity to devote full-time to their development as independent cancer investigators. Applicants must demonstrate appropriate scientific experience and achievement and must have outstanding research potential. Each candidate must be nominated by his/her sponsoring institution. The salary support is set individually with a maximum of $30,000 each year.

	Number Awarded
Cancer Etiology and Prevention	88
Cancer Detection and Diagnosis	5
Cancer Treatment and Restorative Care	13
TOTAL	106

Research Career Awards

This program provides an annual salary of $25,000 to selected cancer investigators for the duration of their research careers. No new awards have been made since 1964. NCI presently makes five such awards annually.

Clinical Cancer Education Program

In 1974 the Clinical Cancer Education Program was initiated under the present guidelines. The purpose of the grants are: (a) to encourage planning and development of educational programs aimed at the ultimate achievement of optimal care of the cancer patient; (b) to enable students in the health professions to acquire basic knowledge of neoplastic disease and of preventive measures, and diagnostic and therapeutic skills and experience in optimal care; (c) to stimulate and expand efforts in cancer education and teaching which will be relevant to changing needs in medical education. Applicants are from medical schools, dental schools, schools of osteopathy, specialized cancer institutions, principal

affiliated hospitals of medical schools and schools of public health. Usually, there is only one award per institution for this program. The object of this support is to provide new curricula for the teaching of students, house officers, nurses, etc. Continuing education in oncology for practicing physicians is also an important part of the program.

There are presently 74 active clinical education grants. In addition to the 74 grants, a contract with the American Association for Cancer Education was completed. The purpose of that project was to develop a methodology for the systematic evaluation of the effectiveness of Clinical Cancer Education Grants. The recommendations are: (a) the development of program goals and cancer educational objectives for physicians and dentists in training (b) the development of new data forms for recording the activities supported by the grants; (c) proposal of two alternative systems of data storage and retrieval to handle information and document the achievements of the clinical cancer education program.

Cancer Prevention Education

Thirteen contracts were awarded in 1979 for the development of courses in cancer prevention. The major objective of twelve of them was to develop and evaluate course(s) in cancer prevention within three years. This objective was accomplished by several means such as: development of audio-visual aids, course modules, case presentations, supplemental reading lists, self-instructional materials, examinations, guidelines for instructors. A thirteenth contract involved fostering cancer prevention and detection through public education and school health education.

The final products of the contracts are presently being reviewed by consultants and NCI staff. After the evaluation is complete, the material will be made available to interested institutions/universities by the contractors and the NCI.

Categorization of the thirteen contracts are as follows:

Occupational Health, Smoking, Breast Self-Exam.	1
Education for Medical Students	4
Education for Medical Students & Residents	3
Nurse Practitioner	1
Nurse Practitioner & Physician Assistants	1
Physician Assistants	3
Total	13

Short-Term Research Training

Short-Term Research Training is of two kinds. The first kind, a program for Students in Health Professional Schools (T35), was designed to ameliorate the shortage of clinical investigators by attracting highly qualified medical students into biomedical and behavioral careers. Funding was made to the University of Chicago in July 1980 for five years. The award was made to support 26 medical students each year for three months. The second kind consisted of targeted short courses up to one week in duration which are offered

to all National Cancer Institute research trainees. These courses include a) Epidemiology, b) Histopathobiology of Neoplasia, c) Culture of Macrophages and Human Monocytes.

Veterinary Pathology Training Program

This program was initiated in 1980. The purpose is to increase the production of board-certified veterinary pathologists, and otherwise to increase the national pool of comparative pathologists. The National Cancer Institute in conjunction with the National Institute of Environmental Health Sciences supports five grants. Two of these are funded by NCI. This program will expire at the end of the present project period.

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